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COMMUNICATIONS

THE UNDERLYING CAUSES OF GLAUCOMA

Including notes on the lines of enquiry which have been pursued, with suggestions as to future research in clinic and laboratory

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(THE MIDDLEMORE PRIZE FOR 1939. THE AUTHOR'S MOTTO WAS "*Pen Goch*")

THE study of glaucoma has occupied and puzzled ophthalmologists for many generations but it is only in the last fifty years that substantial progress has been made in the solution of the pathology of this symptom-complex. That this should be so is due to the increased information which has recently become available in the realms of biochemistry and biophysics, subjects which promise to govern the further approach to the problem and maybe will solve its mysteries.

Historical Survey

Knowledge of the condition of the eye has been limited through all time by the facilities available for the examination of that organ, and in the history of the study of glaucoma this is especially pronounced. The earliest physicians, whose observations were

limited to the outward visible parts of the eye, were only able to distinguish between amaurosis with cataract and amaurosis without. The derivation of the word glaucoma is from the Greek and the early Greeks themselves distinguished the forms of amaurosis by the colour of the pupil. Hippocrates refers to glaucosis, in which the pupil becomes blue-green in colour, in these words: "If the pupil become sea-coloured, sight is destroyed and amaurosis of the other eye often follows." This description, however, shows no appreciation of the differentiation of glaucoma as we now know it from other forms of amaurosis. The first mention of increased intra-ocular tension appears to have come in 1348, from Sams-al-din who was an Arab and a voice crying in the wilderness, for his observation remained neglected for nearly three hundred years. In 1626 Richard Banister described a form of gutta serena which was characterised by long duration, hardness of the eyeball, no perception of light, and no dilatation of the pupil if the other eye were bandaged. In his opinion this condition was incurable. The same four points occur in "A treatise of the Eyes" by Sir William Read, oculist to Queen Anne, undated but probably 1706, and he also mentions the good results of performing a limbal puncture or posterior sclerotomy on a case of glaucoma, one Jeremiah Puttiford in 1705. He held that glaucoma "proceeds from the viciated crystalline humour." According to Sorsby (1932) the reference to the four cardinal points is "lifted" from Banister's treatise, but the case reference is Read's own and is amusing reading though somewhat boastingly phrased. Again these observations received no general acceptance and were not re-discovered till Johann Platner in Germany referred to increased tension of the eye in 1738. From now on, interest in glaucoma became common, and increasingly accurate observation made clear successively the structural changes of glaucoma in its absolute state. Demours (1762) added the recognition of the symptom of rainbow-coloured rings, while Desmarres and Mackenzie both advocated the operation of paracentesis as a method of treatment. The invention of the ophthalmoscope by Helmholtz (1821-1893) in 1851 led to the observation by Jaeger, in 1854, of changes in the optic disc which he thought to be swollen, but Weber (1856) correctly described the cupping of the papilla. De Wecker considered that glaucoma consisted of a disturbance of equilibrium between secretion and excretion of fluid inside the eye, and his operations of iridectomy and sclerotomy were designed to facilitate the escape of fluid from the eye. Lange (1912) was the first to demonstrate diminution of intra-ocular tension following the use of miotics. At this stage the study of glaucoma widened into innumerable explanations of various features, symptomatic and structural, but always the

ultimate factors responsible have eluded discovery. The fact that the disease, or diseases, included under the name of glaucoma are frequently insidious in onset accounts for this in large degree, since the disease is usually well advanced when first observed, and is terminal when opportunity for pathological investigation presents itself, except in some cases of glaucoma associated with intra-ocular growth.

In considering therefore the underlying causes of glaucoma, it is essential first to define by elimination many of those changes which have in the past been held to be the causal agents. Indeed it would seem that, as investigation advances and knowledge increases, the causes become ever again results of more deeply seated cause and their true origin recedes yet further into the obscurity of the unprobed mysteries of medicine.

The theory of chronic inflammation as the cause of glaucoma was one of the earliest to be held since glaucoma secondary to iritis was recognised, long before the discovery of glaucoma simplex as a clinical entity. William Lawrence, Beer and Demours reflect this general opinion of ophthalmologists of the eighteenth century. It is now plain that the exudates produced and adhesions formed inside the eye in certain inflammatory states produce obstructions which interfere with the normal equilibrium of drainage of intra-ocular fluid and illustrate only one method by which the symptom complex of glaucoma may be arrived at.

The discovery of glaucoma simplex, a condition of raised intra-ocular tension without antecedent inflammation, which was established during the nineteenth century, resulted chiefly from the invention by Helmholtz of the ophthalmoscope, which enabled the ophthalmic surgeon to see the changes in the optic nerve head. This discovery led to the supposition that cupping of the disc was the result of the raised intra-ocular tension and attention was henceforth directed to the causes of this rise of pressure.

Theories on the cause of increased intra-ocular tension in primary glaucoma.—Hypersecretion of intra-ocular fluid was the first suggestion: depending on the assumption that the major changes were to be found in the amount of aqueous humour, it was put forward by von Graefe (1855) that, in glaucoma, the increased tension was accounted for by a congestive condition deriving from a chronic inflammation of the iris and ciliary processes: he and De Wecker presupposed a serous choroiditis as the underlying cause of the increased fluid content of the eye, and noted that this could happen without visible changes occurring in the fundus. De Wecker postulated a disturbance of the balance between the equilibrium of secretion and excretion of the intra-ocular fluid, and remarked that in glaucoma the disturbance was of rapid onset. Donders (1862) ascribed the hypersecretion of

fluid to nervous irritation of the choroid; this theory was not favourably received at the time but the most recent work on this problem indicates that it has much to commend it in relation to the admitted importance of a nervous diathesis in this disease. These theories, however, all give only a partial explanation of the rise of tension and leave unexplained the deeper causes.

Theories of *excessive retention* of the intra-ocular fluid were at first dependent on alterations of the anatomical structure of the eye in glaucoma observed in life and after enucleation. In respect of the latter in particular the changes were almost always advanced and with regard to the former usually so. Bowman (1862) considered that there was in glaucoma a disproportion between the size of the eye and of the lens, the latter being either over-large or the former unduly small. This thesis was given further impetus by the work of Priestley Smith who, from 1907-1912, published a series of papers (Glaucoma Problems) on his researches into glaucoma simplex. He emphasised the progressive increase with age of the size of the lens and ascribed the onset of glaucoma to narrowing or obstruction of the space between the lens and the ciliary processes, and in this connection suggested that sudden congestion of the processes might be the determining factor. He considered the excretion of aqueous to be governed by the condition of the filtration angle and of the iris crypts, and believed that closure of the filtration angle was either complete or partial in all cases of primary glaucoma. This, he maintained, was achieved by a forward movement of the iris and lens as a single mass following the obstruction of the circum-lental space. He supposed an increase of vitreous pressure due either to compression of the vitreous by an increased volume of the uveal tract, to defective filtration between the vitreous and aqueous from closure or restriction of the circum-lental space, or to an increase of fluid content of the vitreous itself. (Ref. 1911 p. 98-99 Ophthal. Rev.) In respect of the relatively higher incidence of glaucoma in hypermetropic patients Priestley Smith claims that there is relatively a larger lens in a small eye in such cases, and gives measurements of the average sizes of the corneae in healthy and glaucomatous eyes showing the latter to be definitely smaller.

Changes in the state of the pectinate ligament were brought forward by Thomson Henderson (1910) who observed sclerosis of the trabeculae in old age and has advanced the theory that sclerosis at this site is primarily responsible for the rise of tension in primary glaucoma by obstructing the outflow of aqueous to the canal of Schlemm. Verhoeff (1915) also subscribed to the hypothesis of sclerosis of the pectinate ligament and submitted that this resulted from the formation of peripheral anterior synechiae. Obstruction of the filtration angle by deposits of

pigment granules and flakes off the anterior lens capsule have been observed by Koeppe (1916) and Barkan (1936), and these authors submit that these particles constitute an important factor in the determination of glaucoma.

Both those who believed in a basic hypersecretion of intra-ocular fluid and those who asserted some structural alteration within the eye as a cause of retention of intra-ocular fluid have equally maintained that the atrophy of the optic nerve found in glaucoma was the result of the increased intra-ocular tension as such. The lamina cribrosa which normally presents a straight line continuous with the curve of the sclera is sharply curved back with a concavity towards the vitreous (Parsons 1905, and others), but the possible influence of pressure in producing a progressive degeneration of the retina through chronic or intermittent ischaemia was admitted. In marked contrast, Schnabel (1892) considered that there was an active atrophy of the nerve and that this was shown by the formation of new vessels and the proliferation of interstitial connective tissue. He maintained in his description of the formation of lacunae in the optic nerve that the lamina cribrosa is not pushed back, but is pulled back by shrinking of the connective tissue of the nerve in its retro-ocular part.

During the nineteenth century and first decade of the present century, when the structural changes in glaucomatous eyes were receiving so much attention, other factors were somewhat summarily set aside as predisposing or exciting causes. This was partly due to lack of information as to the condition, normal and pathological, of the intra-ocular fluids, and to ignorance of the vascular changes dependent on nervous stimulation or on hormonic and metabolic influences. Of the predisposing causes emphasis has been laid on dilatation of the pupil by atropine which, according to Parsons (1905) and many other authorities, results in the mechanical obstruction of the filtration angle by the thicker iris being crowded up towards its root. It is interesting to record, however, that Wessely (1900) noted that dilatation of the pupil was accompanied by a fall of tension following subconjunctival injection of suprarenin.

However, the importance of vascular changes was not entirely ignored, but rather considered of secondary significance, by the investigators of thirty years ago. The preponderance of primary glaucoma in women, the influence of excitement, grief and other emotional upsets, and the relation to other congestive factors were duly noted, but their true significance was not fully appreciated at that time.

Recent Theories

The most striking change in the study of glaucoma in the past twenty years has been the wide attention given to the condition of the general and local vascular and lymph systems. Increased facilities for investigation have brought to light the laws governing the passage of various groups of substances in the plasma through the capillary walls and the mechanism of semi-permeable membrane dialysation. The researches of Lewis and others have revealed the nature of local alterations of the capillaries in response to the stimuli of heat and cold, the presence of vaso-motor nerve control, both dilator and constrictor, and even of an entirely separate nervous control system in response to trauma. (1937.)

Dale and his co-workers have shed light on the presence of active substances in the tissues and in the blood, and have shown the chemical nature of nerve transmission, a theory propounded first by Loewi (1921) and Cannon (1932), and followed by the researches of Dale, Carmichael, Fraser and others. Acetyl-choline has become a power of double force as the conveyor of both vaso-dilator and vaso-constrictor impulses and the function of eserine has been lowered from its former position as the constrictor of the pupil to the protector of acetyl-choline. This turning towards the blood, its vessels, its nerves, its contents and its biochemical and biophysical properties has resulted in a re-orientation of the conception of glaucoma based on the blood and tissue fluids.

In the first place the theory that the aqueous humour is a secretion derived by glandular activity on the part of the ciliary processes' epithelium gave way to that of dialysation. The experiments of Duke-Elder claimed to show that, in most particulars, the aqueous humour was composed of a dialysate from the blood plasma through a semi-permeable membrane, the capillary walls, and that the proportions of colloids, electrolytes and non-electrolytes followed precisely the laws governing such a passage. Hence theories based on hypersecretion of intra-ocular fluids gave place to those based on alterations of capillary permeability. Recent work by Robertson (1937), however, goes to show that secretion in some degree must take place since it has been found "*that neither water, dyes nor electrolytes can permeate the membrane of the posterior chamber in the reverse direction*" (Friedenwald and Pierce 1931). His experiments on the relation between the intra-ocular pressure and the osmotic pressure of the plasma following injections of hyper-, hypo-, and iso-tonic saline, and varying concentrations of gum arabic, intravenously, also prove that the aqueous humour in many respects does not behave like a true dialysate. It has become apparent now that primary

glaucoma is essentially a symptom complex of vascular origin and that it represents a local manifestation of a general vaso-motor disturbance.

The Underlying Causes of Glaucoma

The hypothesis put forward in this essay is that the causes of primary glaucoma are those of capillary and venous stasis, and that the condition arises from the changes resulting from such a disturbance of the local circulation. Secondly it is held that the symptom complex known as glaucoma includes a number of separate conditions whose only features in common are those represented by ultimate decompensation of the mechanism provided for the excretion of fluid from within the eye. Thirdly it will be shown that primary glaucoma or glaucoma simplex is the local manifestation of a general disease or, in the words of Lagrange (1922), that " The eye attacked by hypertension is a sick eye in a sick body and is not merely a hypertonic organ but also a sclerosed and dystrophic organ that shares the trouble with the rest of the body."

Inflammation and glaucoma.—It is well established that acute inflammation does not produce more than a fractional rise of tension. Thus, even in those cases of iritis where the aqueous humour becomes turbid with white blood cells, or is filled with a dense gelatinous exudate, the eye never becomes more than slightly tenser than normal; a tension exceeding 30 mm. Hg is not found. When it is remembered that, in such cases, there is almost always a co-existent increase of vascularity in the remainder of the uveal tract, the ciliary processes and choroid, it becomes obvious that the increase of the vascular bed within the eye must be enormous. That no increase of tension occurs is due to the fact that there is no circulatory stasis and that the blood flow is not slower than normal but faster. It must further be emphasised that although the aqueous becomes excessively albuminous in content and may contain large numbers of white or red blood cells, these conditions produce no embarrassment of the filtration angle. What Duke-Elder has termed the plasmoid aqueous of inflammation does not give rise to obstruction or to rise of tension. This point indicates that obstruction of the filtration angle by pigment cells and flakes from exfoliated lens capsule does not in fact occur but that such cells are found congregated in the trabeculae of the pectinate ligament, not because they have obstructed the spaces of Fontana, but because the rate of flow from the canal of Schlemm, through the ciliary processes and episcleral veins, is sluggish : leaves do not obstruct a stream but

collect on the surface of quiet pools. The increased production of aqueous is easily passed away in spite of the increased viscosity; in some cases the gelatinous exudate filling the anterior chamber can be seen to be removed within twenty-four hours. Only in the presence of stasis of the circulation in the capillaries and veins does inflammation produce obstruction, hence the benefit resulting from the use of leeches or other de-congestive treatment in obstinate cases.

The adhesions produced by repeated attacks of inflammation, particularly those between the lens and the posterior surface of the iris, may, however, restrict the forward movement of the aqueous from the posterior to the anterior chamber, while the formation of a layer of exudate in the layers of and between the fibres of the suspensory ligament of the lens may prevent the exchange of fluids between the vitreous and the aqueous. In such circumstances increased tension may result from mechanical obstruction and a condition of secondary glaucoma is established. The bowing forward of the aqueous behind the iris in cases of ring synechiae is the expression of the greater amount of fluid derived from the increased vascularity of the choroid and ciliary processes, which constitute by far the greater part of the vascular bed. The increased tension in such cases is relieved by broad iridectomy, which breaks the ring of synechiae and re-opens the way between anterior and posterior chambers. In such cases this procedure provides a permanent cure of increased tension provided that further exudates do not block the iridectomy.

Glaucoma in Association with New-growths

It has been stated (Dunnington, 1938) that in the early stages of intra-ocular sarcoma the intra-ocular tension is lower than normal. The factors which govern the onset of increased tension are not those of volume and displacement of other intra-ocular contents as may be observed from any series of intra-ocular growths. In some cases increased tension occurs relatively early, in others relatively late. The difference lies in the position of the tumour: those situated at the posterior pole or in the posterior half of the globe are slow to produce raised tension: those which obstruct the venous return from the eye by their encroachment upon the ciliary body or the vorticose veins produce early rise of tension. It has been observed for many years that tumours of the ciliary body (chiefly melanotic sarcomata) frequently produce also obstruction of the filtration angle in that region leaving the opposite part freely open: (Figs. 1 and 2).

This anatomical displacement has been cited as the cause of glaucoma (Priestley Smith), but Parsons states that proximity to a vortex vein and obstruction of venous return is the most important factor. That the pressure of a detachment of the retina

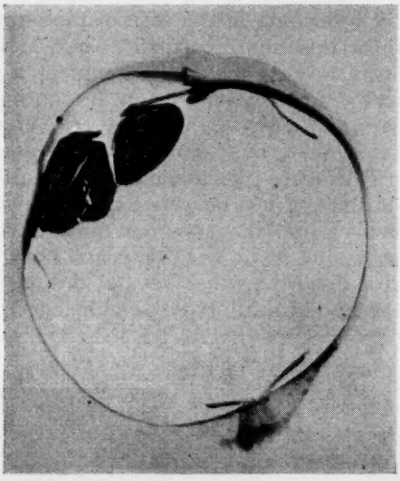


FIG. 1.

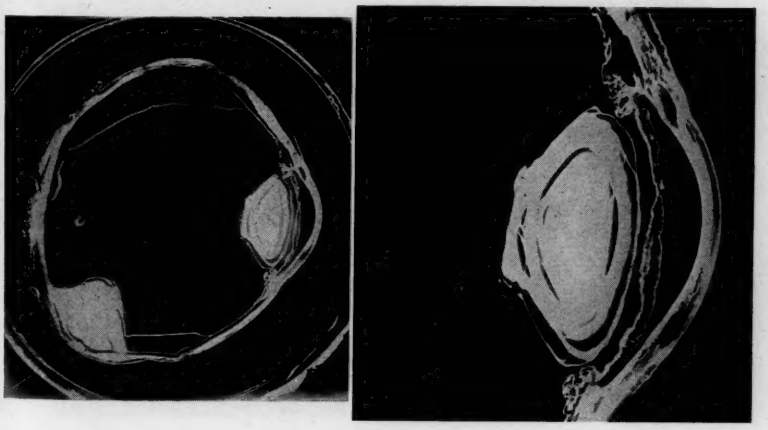


FIG. 2.

overlying the growth might throw the vitreous and the iris-lens mass forwards was suggested by Priestley-Smith (1891) but this is no longer seriously entertained since it is found that the size of the detachment bears no relation to the tension, while, in detached retina due to other causes there is notably a tendency for the intra-ocular pressure to be low. The true mechanism of the early onset of glaucoma in the case of tumours in the ciliary region is seen to be the interference with the venous return from that part. In this way alone can be explained the transitory incidence of attacks of increased tension alternating with periods of freedom, sometimes for years, in the presence of a progressively increasing mass. One recalls to mind a patient (W. T.), who suffered an attack of acute glaucoma in 1925, and was then free of symptoms till 1928, when he suffered a further attack. The melanotic sarcoma of his ciliary region must have been getting progressively larger during those three years, but gave no trouble till a further factor disturbing the vascular drainage from his eye precipitated the second attack. However, the effect of interference

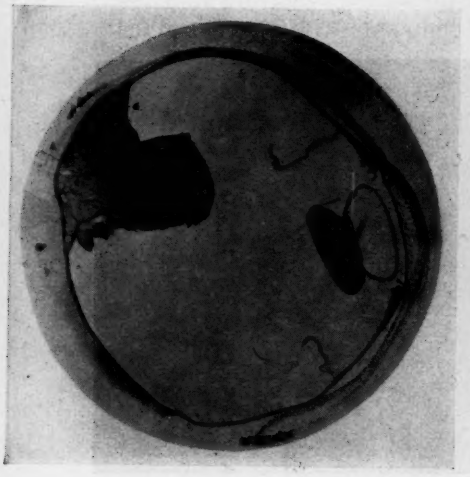


FIG. 3.

FIG. 4.

Mc.L.—Intra-ocular tumour: tension raised. Perivascular infiltration.

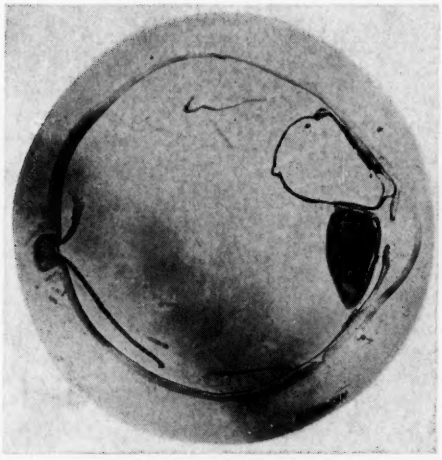


FIG. 5.

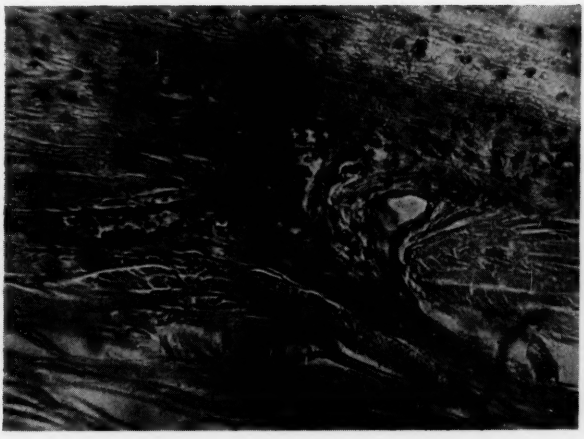


FIG. 6.

Case: Mrs. L.—Cyst of ciliary processes with glaucoma. Marked perivascular infiltration.

FIG. 10.

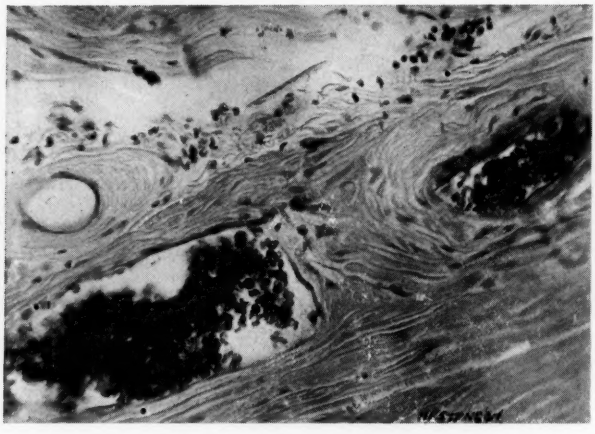


FIG. 11.

Case L.— Large intra-ocular growth : no rise of tension.
Absence of perivascular infiltration.

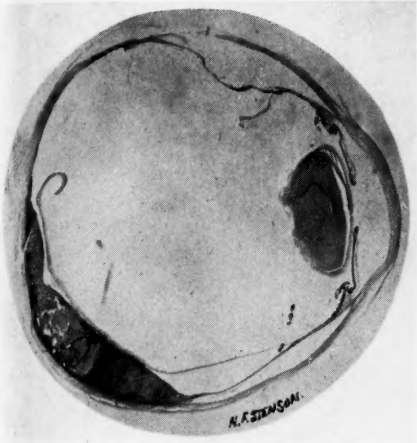


FIG. 12 FIG. 13.

Case : Mrs. B.—Intra-ocular growth : without increased tension.

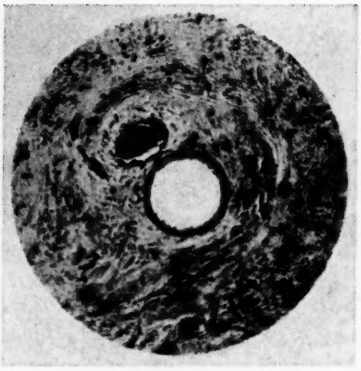


FIG. 14.

Thrombosis of central retinal vein and thrombotic glaucoma (cross-section of optic nerve).

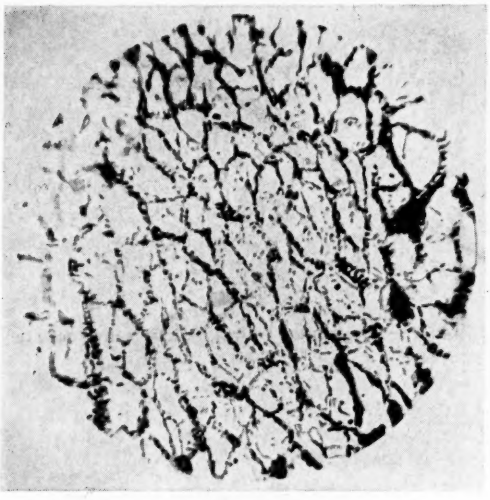


FIG. 15.

Pickworth's stain: capillary stain of optic nerve: fairly normal supply: from acute glaucoma but without thrombosis.

with the venous drainage of the ciliary processes does appear to predispose to early rise of tension in combination with other causal factors of glaucoma: thus, while actual displacement volume is probably of little importance, obstruction of venous return is of the greatest significance. With obstruction of capillary and venous flow come secondary changes of which the most notable is the presence of venous peri-vascular infiltration by small white blood cells. Thus it has been possible to identify

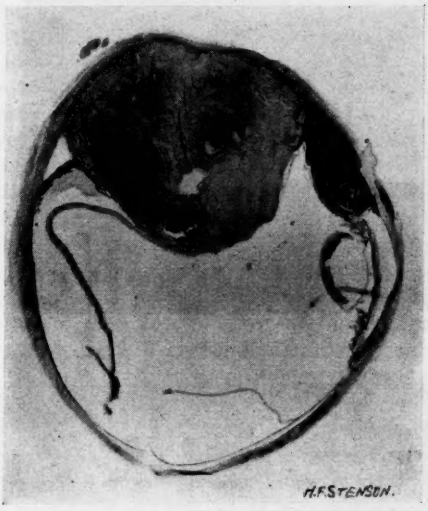


FIG. 7.

microscopically, in eyes removed for the presence of intra-ocular new growth, those in which, during life, there was an increased intra-ocular tension and those in which there was not. Selecting at random some twelve eyes removed for this reason it was constantly found that perivascular lymphocytic infiltration, particularly of the anterior ciliary vessels in the region of the ciliary body and the adjacent areas (Figs. 3 to 6), occurred in those cases where there was a raised tension during life. Conversely one saw examples of very large intra-ocular tumours which although occupying the ciliary region (Fig. 7 to 13), showed no perivascular lymphocytic infiltration of the neighbouring veins: in these there was no rise of tension during life.

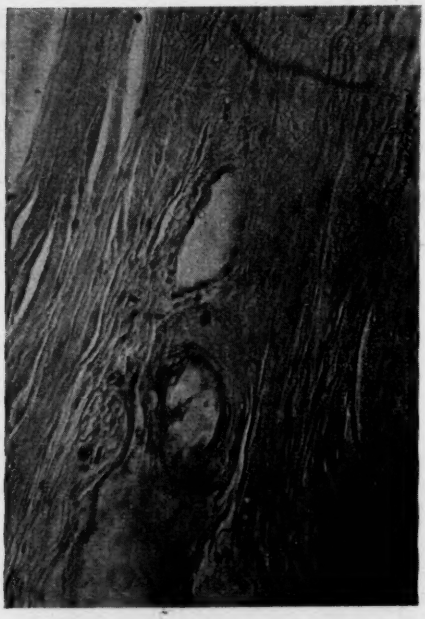


FIG. 8.

FIG. 9.

Case B.—Large intra-ocular growth : no rise of tension.
Absence of perivascular infiltration.

The Vascular Basis of Primary Glaucoma

In considering this condition it is justifiable to separate in the first place glaucoma with increase of intra-ocular tension from that without increased tension.

Dealing therefore with primary glaucoma with raised tension, as being the commoner condition, one has to seek an explanation of the signs and symptoms of the clinical picture, and of the structural changes which have already been excluded as causes *per se*. The hypothesis put forward in this essay maintains that the underlying cause of glaucoma is essentially one of defective vascular nutrition and that it is the capillary and venular portion of the circulation which is for the most part involved. The evidence in favour of such a cause is diffuse, and some of its aspects are not yet clearly understood, but it is justified by giving adequate explanation for the clinical picture.

The long recognised effects of atropine and eserine respectively in cases of glaucoma have usually been explained on the grounds of the alteration in the size of the pupil (Parsons, 1905, vol. III). It has been held that an increase of tension may be initiated by or may be increased by the use of atropine on account of the bunching up of the iris into the filtration angle. This may be a contributory factor but it is probably of relatively slight importance in contrast to the effect of atropine on the whole circulation of the uveal tract. It will be remembered that adrenalin, which also, though to a lesser degree, produces dilatation of the pupil, has frequently been noted to produce a lowering of tension. Further Thiel (1922) has observed acute glaucoma in cases of aniridia. It has been advanced that in such cases of aniridia there is a minute stump of iris root remaining and that this is found to be adherent to the ligamentum pectinatum thereby causing complete obstruction of the filtration angle. But Thiel also found (1922) that pilocarpine produced its usual effect of lowering the tension in these cases of aniridia. Thus the obliteration of the filtration angle is not the deciding factor, but the effect of these drugs on the uveal circulation is paramount. Adrenalin produces contraction of the arterioles, temporarily at least, thus reducing engorgement, but its value is largely offset by the secondary congestion which follows its use. Furthermore the action of adrenalin is not always constant, particularly in regard to capillary effects. (Krogh, 1922.) The action of eserine is that of para-sympathetic stimulation producing increased flow by dilatation of the arterioles, while atropine is its direct antagonist. The function of acetyl-choline or its derivative doryl (carbaminoyl-choline chloride) is also to increase the flow of blood by vaso-dilatation, but these substances will receive fuller consideration

later in connection with other aspects of the problem. Suffice it to say that the contraction of plain muscle tissue, whether innervated by sympathetic or parasympathetic, is now considered to be due to the liberation of acetyl-choline locally and between the nerve-endings and the effector cells.

A further important influence of these drugs on the uveal circulation arises indirectly from their action on the ciliary muscle. The circulation through the system of anterior ciliary vessels, and particularly the question of venous return from this region is largely bound up with the pumping action of the ciliary muscle whose fibres encompass these vessels about and by whose movements the circulation is largely assisted. Paralysis of the ciliary muscle by atropine and its related drugs is a potent factor in establishing stasis in this the major vascular area of the uveal tract. Eserine, pilocarpine and acetyl-choline on the other hand stimulate and assist the venous return from this area. The action of atropine is to neutralise the effects of these drugs by preventing the passage of the stimulus from the acetyl-choline, which exists between the nerve ending and the effector cell (Fraser, 1938), to the plain muscle of the blood vessel wall.

The primary effect of these drugs then is the manner in which they alter the rate of the uveal blood flow.

Further factors in the production of capillary and venous stasis.—The fact that primary glaucoma, particularly the acute congestive form, is predominantly found in women in middle life has already received comment from numerous authorities (Priestley Smith, Parsons and others), and it has been freely admitted that this susceptibility is due to emotional instability. Priestley Smith in an analysis of a thousand cases of glaucoma found that the disproportion between men and women in chronic, non-congestive, glaucoma was not so great as in the congestive type of the disease. The emotional nature of many attacks is also emphasised (Sonder, 1906) by the case of de Wecker in which a woman who was addicted to gambling, and had already lost one eye through glaucoma, went blind in her only eye as the result of an acute attack following a visit to the tables at which she lost heavily. Instances of the onset of acute congestive glaucoma in relation to grief and bereavement are extremely common and well recognised. The mechanism of the " trigger action " of the onset of these acute congestive attacks is to be found in disturbance of the normal balance between sympathetic and parasympathetic control of the intra-ocular circulation, with preponderance of sympathetic irritation and consequently with dilatation of the capillaries and congestion of the uveal tract. The sudden depression of tone in the uveal capillaries and venules initiates a stasis which is the beginning of the establishment of the vicious circle

of events which we recognise clinically as acute glaucoma. The influence of the sympathetic nervous system on intra-ocular tension has received further corroboration from studies of the cervical sympathetic cord, and of the superior cervical sympathetic ganglion. Extirpation of the cervical sympathetic was observed to result in a lowering of tension as far back as 1727 (Pourfour-du-Petit), was suggested as a therapeutic measure for glaucoma by Abadie (1898), and was actually carried out with success by Jonnesco and others about 1900.

The influence of antidromic impulses and of the long axon reflex must also be considered, particularly in relation to the presence of septic or other irritative foci in the distribution of the fifth nerve, and to lesions of the Gasserian ganglion. The complication of increased intra-ocular tension in cases of herpes zoster ophthalmicus gives an example of the former, while the influence of axon reflexes is found in the association between glaucoma and unerupted wisdom teeth, apical dental sepsis, etc. The mechanism of the latter cause of vaso-dilatation is discussed by Jameson Evans (1933 : 1938) in detail, and that there is also an increased permeability of the capillaries due to the production locally of H-substances has been shown by Lewis and Marvin (1927). Woollard (1928) showed that these responses were quite independent of sympathetic nervous stimulation. Further Badal (1883) demonstrated relief in cases of glaucoma by avulsion or tearing of the nasal nerve, as also did Abadie (1883) by stretching or tearing.

A further factor in the question of control of the tone of blood vessels, and one which is not yet fully understood or appreciated, is the action of hormones. Many cases of glaucoma exhibit a generalised upset of vaso-motor tone in association with the menopause or its after effects. Flushes of the skin of transitory nature, palpitation of the heart, particularly due to short attacks of auricular fibrillation or to extra-systoles, and migrainous attacks, are the common companions of glaucoma in such cases. The properties of adrenalin are well appreciated but the interactions of the thyroid, supra-renals, and pituitary are not clearly defined. In particular the ever increasing number of hormones deriving from the latter seem to exert an influence on each of the fellow hormone-producing glands, and amply justify the title of " leader of the hormonic orchestra " given it by Langdon Brown. The possible intervention of the hypothalamus in association with the pituitary and the question of the situation here of a sympathetic centre are further unknown, or little known, factors which may have an important bearing. Even so the clinical fact remains that disturbances of emotional equilibrium are productive of failure of vaso-motor control, usually in the direction of loss of

the normal tone of the blood vessels, and that such patients are, par excellence, candidates for acute congestive glaucoma and constitute a glaucomatous diathesis. Instances of this are often found in patients who, while yet in hospital following operation on one eye for glaucoma, suffer a similar attack in the opposite eye. Similar loss of tone is to be found in many chronic and debilitating diseases and here again the frequency of the onset of glaucoma after prolonged and severe illness is notable.

Arteriosclerosis forms a further subdivision of lack of elasticity in vascular tone. The incidence of acute glaucoma increases progressively with the decades of life, except possibly after the age of sixty-five when material becomes more scarce, and the rising index is proportional to the reduced ability to withstand sudden variations of pressure. Particularly the older patients show a greater tendency to that variation of glaucoma which I call thrombotic, depending, as it does, on thrombosis in the uveal tract. This type of acute glaucoma is characterised by its abrupt onset, the extreme degree of vascular stasis and congestion, and the presence of exudates from the iris which form adhesions between iris and lens. It is often most difficult to differentiate such cases from acute iritis. A further distinguishing feature, not surprising when one considers the underlying condition of the vascular bed, is the invariable lack of response to any form of treatment and the frequency of ultimate excision of the eye on account of intractable pain. Some of these cases arise secondarily to a thrombosis of the central retinal vein, after a latent period of a few days to a month following the initial thrombosis. Thrombosis in the retina does not often, of itself, produce any alteration of the intra-ocular tension. The thrombotic group of cases illustrates the grossest defect of the uveal circulation and the last degree of stasis of the blood flow through that tissue.

Turning now to the early stage of the disease, the prodromal stage, one again finds evidence of the basic influence of the rate of the circulation. In the healthy eye there is a small diurnal variation of intra-ocular tension which is highest during the period of three to six o'clock a.m.; that ebb flow of the tide of life. At this time the circulation is at its slowest throughout the body. The earliest indication of a glaucomatous tendency is said to be an accentuation of the diurnal variation of intra-ocular pressure and it is common knowledge that the disease, when fully manifest, has a predilection for this period of the day in incidence of onset.

Evidence of Generalised Vaso-motor Disease

General manifestations of circulatory instability in glaucomatous patients should frequently be found if the hypothesis of a vascular underlying cause is to be accepted. It has already been mentioned

that the nervous or excitable temperament of glaucoma patients has been noted for many years. Donders, von Hippel, von Graefe, de Wecker, and others have all commented on this matter. Recent work has gone further into the connection between glaucoma and general vaso-motor disturbance. In 1929 Schmidt found a generalised disturbance of the capillary system throughout the body in an analysis of 34 cases of glaucoma simplex, and Wegner (1930) found this to be true in 70 per cent. of his cases. Meizaros and Troth found definite structural and functional changes in the capillaries of glaucomatous subjects, and de Saint-Martin and Meriel, by oscillometric observations, showed widespread vascular disorder in twenty-two consecutive cases of glaucoma. Troncoso (1902) suggested that simple glaucoma is a chronic vascular disease and postulated a permanently increased capillary permeability with severe congestion. He further maintained that atrophy of the optic nerve occurred only through malnutrition of the nerve itself or of the retina.

The inter-relation of glaucoma with the vaso-motor disturbances of the menopause and of the post-menopausal period has already been mentioned, as has also the important influence of arterio-sclerosis. In respect of the latter it is significant that of seven eyes excised in the past two months at a large eye hospital three were undoubtedly thrombotic in origin while a fourth was probably of the same nature. (Fig. 14.)

The connection of glaucoma with general disease has recently received further corroboration by its occurrence in cases of epidemic dropsy in India. The writings of Kirwan and Mukerjee (1938) and Kirwan (1936) on their observations bring out a number of points of particular interest. With regard to the changes in the eye they find that there is a great dilatation throughout the uveal tract of the capillaries, without any inflammatory reaction being present. In addition they claim that there is an increased permeability of the capillaries, as is shown by the diminished difference in the osmotic pressures of the plasma and intra-ocular fluids due to an increased amount of protein in the latter. In addition Chopra and De (1937) have found histamine-like bodies in the blood of patients with epidemic dropsy and it is probable that this accounts for the alteration of the uveal circulation and for the increased permeability of the capillaries. The study of epidemic dropsy then introduces the question of the relation of the intra-ocular fluid to the blood plasma and the significance of the condition and properties of the capillary wall.

Bio-physical properties of capillaries and their application to the origin of the intra-ocular fluids have lately been intensively studied. Duke-Elder (1932) put forward the proposition that the aqueous humour was derived from the plasma as a dialysate

through the capillary walls, and that the capillary walls formed a semi-permeable membrane obeying the laws of the Donnan theorem. The work of Wertheimer (1925), however, showed that the concentrations of ions on opposite surfaces of living membranes is not equal, and claimed that the passage of water through tissue membranes is dependent on such difference. Fischer, F. P. (1928) came to the conclusion that the Donnan theorem did not apply to the conditions of the ocular tissues unless those tissues were dead. In a study of the water-binding properties of the uveal tract Fischer (1934) came to the following conclusions:

(1) That the capacity and intensity of water-binding in the uveal tract is less than that of the cornea and sclera but greater than that of the lens.

(2) That the water-binding capacity of the choroid is greater than that of the iris.

(3) That the quality of water-binding in the iris is different from that in the ciliary processes and choroid, there being in the iris more colloid-bound water and in the ciliary processes and choroid more free water.

Friedenwald, J. S., and Stiehler (1938) have investigated the question of the ciliary secretion of aqueous humour and have shown that "there is a barrier between the stroma and the epithelium of the ciliary body which, under asphyxia, exhibits a selective permeability in favour of acid as against basic dyes." The importance of this observation in relation to the pathology of congestive glaucoma is appreciated when considered in conjunction with the clinical and experimental research of Fischer, M. H., and Thomas (1909), and of Fischer, M. H., who demonstrated marked swelling and tension in excised eyes on placing them in a solution containing a trace of lactic acid. Robertson (1937) also came to the conclusion that "a physical equilibrium does not exist between blood and aqueous and that the equilibrium level of the intra-ocular pressure is not maintained by the hydrostatic force in the capillaries minus the difference in osmotic pressure between the aqueous and the blood." Furthermore, Friedenwald and Stiehler claim to have demonstrated the existence of an ionic electric current between the ciliary epithelium and stroma sufficient to provide for these changes. The source of this energy is found in the respiratory metabolism of the tissue, and "is due to the presence in the epithelium of indophenol-oxidase and the absence of this enzyme in the stroma. Dehydrogenases are present in the epithelium and the stroma." This electric current is held to have a secretory function, at least in respect of water carriage, but this realm of investigation is not yet complete.

At present then the capillary wall remains an unscaled obstruction and its properties seem to be less easily revealed than at first appeared probable. It appears then that such an explanation (the Donnan theorem) is insufficient to account for those circulatory changes found in glaucoma.

Again one is forced to consider as additional factors the influence of nervous control or regulation, of local metabolites, and of hormones. It is of some importance to note the, as yet, incomplete investigation of the hypothalamus. It has already been suggested that this region contains centres for a number of basic functions such as the maintenance of temperature or the regulation of sleep. The centre for water-binding has also been placed in the same region and, though the evidence is not yet complete, it may be remembered that this region is intimately associated with diabetes insipidus—another, though opposite, disturbance of water movement.

The result of these various factors, be they central in origin, blood-borne in the nature of hormones or toxins, or the result of nervous impulses from the periphery, is to produce in the uveal tract congestion and stasis, with dilatation of the capillaries and increased permeability of their walls. The research of Latham (1938) on the small blood vessels of the brain claims to show a distinction between what he terms pre-stasis and stasis. According to his definitions the condition of the uveal circulation in the later stages of glaucoma is really one of pre-stasis. Latham states that stasis is a reversible process which is not accompanied by transudation of serum and cells from the blood vessels into the surrounding tissues, whereas pre-stasis with retardation of the blood flow is an irreversible process accompanied by transudation of cells. Clinically the early stages of glaucoma probably involve only a stasis in the uvea but pathological material in this stage is seldom available. Histological examination of eyes enucleated in the later stages of congestive glaucoma shows invariably the presence of perivascular cellular infiltration, a fact which was first noted by Birnbacher and Czermak (1886), who also observed proliferation of the endothelial cells of the veins. Examination of available material has confirmed these points in glaucomatous eyes (Figs. 16 to 17), and the contrast in the findings, in cases of intra-ocular tumour, between those cases in which increased tension was present and those in which it was absent, has already been emphasised. On the other hand, mere congestion and dilatation of the uveal blood vessels (as shown in Figs. 9 and 10), though it was in this case extreme, showed no such changes in the vessel wall, or in the perivascular area. This coincides with the absence of stasis and of tension (Figs. 9 and 10). The histology of the optic nerve capillaries will be discussed in connection with the question of optic atrophy.

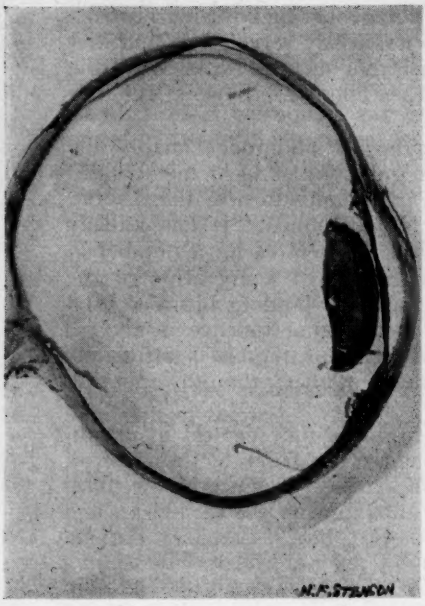


FIG. 16.

Case: Mrs. R.—Acute glaucoma.

FIG. 17.

Perivascular infiltration.

Contributory Factors.—While it is probable that the underlying cause of glaucoma is essentially an arteriolar and capillary stasis of the uveal circulation there are a number of predisposing and contributory factors which need to be mentioned and their importance must be duly assessed. Many of these will be seen to have been considered direct causes of glaucoma in the past; as is the common fate of all but the most essential truths in the course of progress, these now give place to deeper root causes. These contributory factors concern solely glaucoma of primary type, acute congestive or chronic; the secondary glaucoma following frank inflammation of the uvea is hardly in dispute as regards its mechanism. Having regard first to anatomical changes in the eye the most important probably is the proportionate size of the lens to the eye as a whole. Bowman (1862) held this to be a major factor in glaucoma and Priestley Smith (1887) also drew attention to the matter in his papers on " Glaucoma Problems " between 1910-1912. He emphasised that this disproportion reduces the space between the lens and the ciliary processes through which space must occur the exchange of substances between the aqueous

and vitreous. In addition he mentioned the smallness of the hypermetropic eye and the hypertrophy of the ciliary muscle through continuous accommodation, and the fact of the steadily increasing size of the lens as life advances. These facts must be admitted and there can be no doubt of the importance of certain anatomical tendencies as predisposing to the incidence of glaucoma in those eyes which are on the verge of it, or in aggravating and maintaining the disease when it has once occurred. Magitot has stressed the importance of the " terrain malade," but, given this, the form of the eye is of great significance.

Thomson Henderson (1910) carried out investigations on the structure of the pectinate ligament and concluded that sclerosis of the trabeculae occurred constantly, though in varying degree, with advancing age. He considered this phenomenon to be a major factor in producing retention of the aqueous humour and the production of glaucoma with increased tension. More recently deposits of pigment granules have been found in excess in the meshes of the pectinate ligament and in the angle of the anterior chamber in cases of glaucoma (Koeppe, 1916). Exfoliation of the anterior lens capsule has received attention from Vogt (1925) and in 1932 Sobhy Bey drew attention to its association with glaucoma, as also did Horven in 1937. These flakes are rubbed from the surface of the lens capsule by movements of the iris and then pass to the filtration angle which they appear to obstruct. Mallin, however, states that these flakes do not, in fact, block the filtration angle. This process of scruffing of the periphery of the anterior lens capsule is considered by Scandinavian authorities to indicate an underlying chronic uveitis which they consider to be the cause of glaucoma. These changes may provide additional factors favouring the onset or maintenance of glaucoma in predisposed eyes but cannot be considered as causes of glaucoma *per se*. It must be noted with regard to sclerosis of the pectinate ligament in old age that this change occurs in equal degree in the non-glaucomatous senile. In respect of exfoliation of the lens capsule, this process, in its origin, is determined by degeneration of the capsule, a process which is very probably due to an excess of toxic metabolites in the aqueous and to their prolonged retention on account of venous and capillary stasis in the canal of Schlemm system and the ciliary region.

Ever since Leber in 1873 discovered that the aqueous was drained from the eye in the angle of the anterior chamber, the condition of the filtration angle of the canal of Schlemm has been a constant study. It has been said that closure of the filtration angle is the cause of glaucoma, the mode whereby the safety-valve mechanism for the removal of the intra-ocular fluids was disorganised. Knies (1876) believing in an

inflammatory condition, and Weber (1877) asserting the effect of forward pressure by swollen ciliary processes, were amongst the earliest to observe obliteration of the angle of the anterior chamber in glaucomatous eyes after excision. Priestley Smith (1910) dealt with the microscopic anatomy of the filtration angle in eyes excised for glaucoma, and showed that obliteration was almost invariable in these cases. Although the pathological material was almost always in a terminal stage of glaucoma it came to be assumed that the condition of the filtration angle would be similar, if not identical, in the early stages of the disease. The advent of the gonioscope, however, dispelled this error and it was shown by Thorburn, Troncoso and others that, in the early stages of glaucoma, there is frequently no obliteration of the filtration angle. Hence it has become clear that closure of the angle is a secondary result of glaucoma, though a complication of great importance. That interference of the filtration angle is a severe embarrassment in an eye predisposed to or threatening glaucoma is not to be denied, however, and we owe much in theory and more in therapy to the pioneers who taught the importance of this structure. Lastly loss of elasticity of the sclera through turgescence, in congestive glaucoma, has been cited as an important factor. The sclera does in fact become turgid but the amount of elasticity in this tissue is minimal even in health, and the sclera itself is probably not of great importance apart from the possible pressure on the vorticose veins passing through it. The accumulation of serum in the supra-choroidal space is more significant, since there forms in this situation a sheet of plasmoid transudation which extends all around the outer surface of the uveal tract and thickens the volume of the coats of the eye considerably. Anyone who has performed a trephine rather too far back will have noticed the escape of serous fluid on reaching the space immediately over the ciliary processes, and the same fluid is to be encountered in the supra-choroidal space in the operation of cyclodialysis. The presence of such an albuminous fluid is shown below (Fig. 18).

Staphylomata constitute an example of the effect of devitalisation of the sclera following its degeneration. This may be due to prolonged stasis and accumulation of toxic waste products within its layers or may be due to actual ischaemic degeneration associated with vascular sclerosis. Since, however, these staphylomata occur chiefly in association with absolute glaucoma with high tension it is fair to assume that such cases belong usually to the stasis group with accumulation of vasotoxic metabolites.

Having considered the anatomical changes which have, in the

past been credited with the causation of glaucoma, and are now considered as only predisposing or secondarily resultant factors, one must review other changes of important association.

The stasis of the uveal circulation results in an accumulation of toxic metabolites of which carbon dioxide, lactic acid and choline are perhaps the best known. These in turn have their effect on the intra-ocular fluids. The changes in the vitreous present a difficult but most important field for research. Alkalinity of the blood may account for glaucoma according to Meesmann (1930) and Biffis (1933) but the researches of Fischer and of Fischer and Thomas (1910) favour the importance of an excessive acidity. Fischer showed that changes in acidity or alkalinity greatly altered the water-binding properties of colloids. Experiments on frogs' limbs, with occlusion of the circulation, showed that the limbs swelled in water due to taking in of fluid: this he accounted for as due to the presence of excess of lactic acid in the limb as a result of the stoppage of circulation. He found that excised eyes of sheep, ox and pig could be made to swell and burst by the addition of minute traces of lactic acid to the fluid in which they were placed. This authority believes that all parts of the eye took part in the process in equal share, but in life conditions are such that the vitreous alone is chiefly exposed to contact with metabolites. Fischer concluded that glaucoma was due to the failure of removal of waste products. He and Thomas were able to lower the tension in cases of glaucoma by giving subconjunctival injections of sodium citrate. The use of calcium salts has also been found beneficial, supposedly through their action in decreasing permeability of the uveal capillaries. In glaucoma of the acute congestive type, with increased intra-ocular tension, it seems clear that mere engorgement of the ciliary processes is hardly enough to account for the forward movement of the iris-lens mass. The only other mechanism possible is an actual enlargement of the vitreous body through an increased adsorption of fluid to its colloid content. It is held that in the normal healthy eye the vitreous is already in a condition of maximum adsorption: this may be so but it is possible that in the presence of an excess of local metabolites it acquires a greater capacity than it can achieve in the normal pH. This may account for the maintenance of tension and resistance as shown by the "bounce" of glaucomatous eyes for some days after excision.

Duke-Elder (1933) found that the vitreous was not a peculiar structure but that similar structures could be produced by other dilute blood-clot gel formations. He maintains that the vitreous is a blood dialysate with the addition of two proteins, the residual protein and the specific muco-protein. The latter, which gives a distinctive band in the spectrum, is easily upset by failure of

oxydation in the vitreous. The alteration of the specific mucoprotein in cases of glaucoma, and the relative albumen content of the vitreous of the glaucomatous and healthy eye need to be closely investigated from this aspect.

The question of the presence of H. substances in the eye has also received attention. Some such substance has been detected in the aqueous by Duke-Elder in experiments on cats and rabbits (1933) in which he induced artificial glaucoma. Ridley (1938) has also shown that in normal tears there is an H. substance which he postulates is neutralised in the healthy eye, possibly in the aqueous. He holds that in the diseased (and glaucomatous) eye this defence mechanism in the aqueous is absent so that free H. substance is then found within the anterior chamber. Friedenwald (1930) was able to show a vaso-toxic substance in the aqueous in cases of glaucoma. These observations all point to the possibility of an association between glaucoma and the axon reflex which Lewis (1927) has shown to result in the triple response with liberation of H. substance in the affected organ. In particular one has to note the frequency of glaucoma originating in peripheral irritation in the fifth nerve area (Sluder and others).

Chronic Glaucoma

Chronic glaucoma, in which symptoms are possibly completely absent till loss of visual acuity and of field of vision are extreme, and in which rise of intra-ocular tension is seldom or never recorded, has always presented a difficult problem. It has been maintained that, in all such cases, there must be raised tension, if not during periods of observation of the patient, at some other period. Such an assertion is of course difficult to refute but the clinical course of many such cases is against such a statement and, in fact, it must be admitted that cases of chronic glaucoma do occur in which the intra-ocular tension is never raised, while others occur in which the intra-ocular tension is rarely and only moderately raised. Magitot (1929) has summed up his own experience in the phrase—" hypertension n'est pas glaucome."

From such cases one passes to subacute glaucoma in which attacks of congestive type alternate with periods of chronic glaucoma during which the tension is not raised abnormally. In chronic glaucoma the characteristic point of similarity to acute congestive glaucoma lies in the optic atrophy with cupping of the disc, and the visual field loss shown especially and initially in the nasal step of Roenne (1909). The absence of the other changes found in acute glaucoma has led many authorities (Duke-Elder, Friedenwald, etc.) to assume that chronic glaucoma

FIG 18.

Serous transudation in the enlarged supra-choroidal space (marked A): section some 5 mm. behind the limbus.

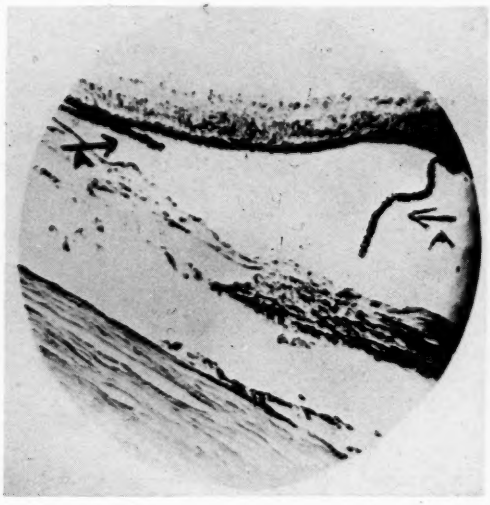


FIG. 20.

Subacute glaucoma: showing degeneration and shedding of the pigment epithelium of the retina (marked A).

is a separate disease entity. However, this is probably not so, in spite of the many differences between the two syndromes, and the intermediate forms of the disease showing both types at different times prove that essentially they are the same. However, it is reasonable to deduce that some of the factors which contribute to the acute syndrome are, in the main, absent in chronic glaucoma. The fundamental and underlying cause, however, remains, namely defective circulation. This is borne out by the work of Lauber (1928) on optic atrophy in which he has shown that the progress of optic atrophy bears a direct relation to the ratio of the systemic blood pressure (and hence of the pressure in the ophthalmic artery) to the intra-ocular tension. Optic atrophy increases when the intra-ocular tension in proportion is raised or when the blood pressure is lowered. The diastolic pressure is of greatest importance in this respect. Troncoso (1902) believed that the optic atrophy of glaucoma was due to degeneration following on chronic vascular disease. Earlier still Schnabel (1892) held that the optic atrophy was due to an essential shrinking

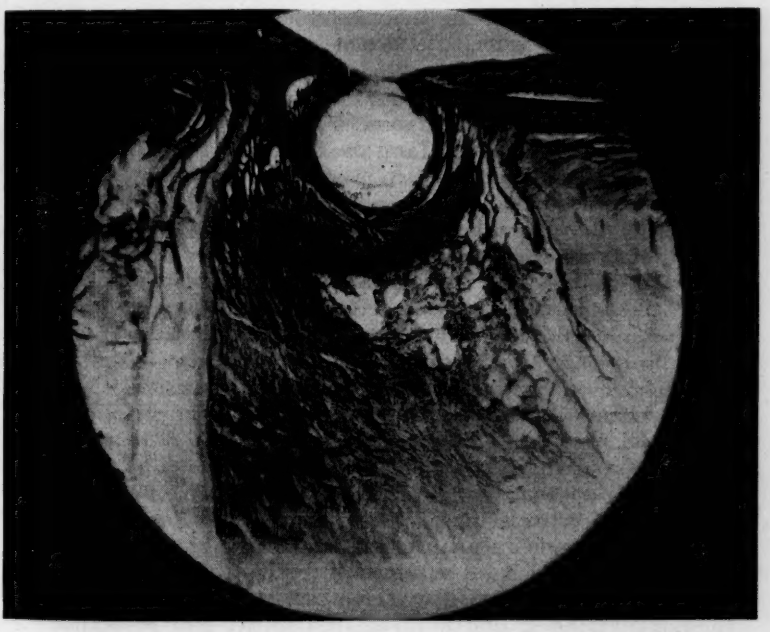


FIG. 19.

Cavernous atrophy.

and not to the effects of intra-ocular pressure, though his contention did not then meet with much support. In this thesis it is held that the optic atrophy of chronic and of acute glaucoma is due to defective circulation involving either an actual ischaemia through sclerosis of the arterioles supplying the retina and optic nerve or to functional ischaemia in which, though the capillaries may be adequate in volume, there is impairment of velocity of the blood flow so that toxic waste-products are inadequately or too slowly removed. There follows then a toxic degeneration without inflammatory reaction which is most marked on the temporal part of the optic nerve and retina, where the major number of nerve-fibres are crowded together, and where the effects of a low degree of oedema exerts a maximal pressure in proportion. Thereby the typical arrangement of nerve bundle atrophy is produced. The histological characteristics of optic atrophy in chronic glaucoma are well shown in the specimen (Fig. 19).

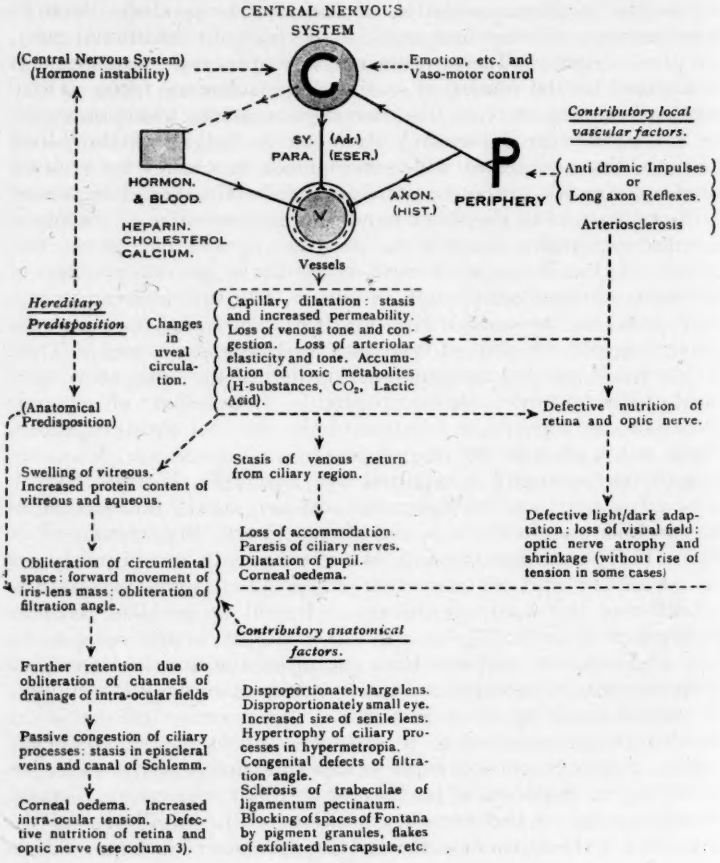
The optic nerve is shrunken as may be seen by the width of the vaginal space: pressure from the inside of the eye cannot produce this picture and indeed compression from the vitreous would tend to thicken the part of the nerve behind the lamina cribrosa. The nerve itself shows well the lacunae formed by the coalescence of vacuoles and there is total absence of inflammatory reaction. The shrinking of the nerve axons allows of a moderate degree of overgrowth of neuroglia which, however, is insufficient to fill the spaces completely. On the same hypothesis may be explained the gradual failure of light and dark adaptation so often found in congestive glaucoma which may be due to atrophy of the pigment epithelium which is dependent on the choroidal circulation for its nutrition: the precise changes are not known but may be largely those of oedema of this layer and of the rods and cones following devitalisation and anoxaemia. Such a condition is seen in this photograph from a case of subacute glaucoma showing the shedding and disintegration of the pigment epithelium (Fig. 20).

The work of Waite, Derby and Kirk (1925) shows that, in early glaucoma, even before the onset of increased tension, the light sense becomes defective both in respect of the light minimum and of dark adaptation. This also favours the theory of insufficiency of the choroidal circulation in early cases. The clinical picture of chronic glaucoma simplex again shows that the difference from the acute congestive syndrome is only one of the relative incidence of ischaemia, rather than of stasis with toxic transudation. In patients of this class the influence of those factors leading to disturbance of the sympathetic-parasympathetic equilibrium, such as emotional changes, and hormone instability, and of peripheral influences giving rise to long axon reflexes and antidromic impulses are of lesser degree or absent, while the factors of

arteriosclerosis or venous endothelial thickening are most marked. Hence it is observed that, whereas in acute congestive glaucoma women are more frequently affected than men, in chronic glaucoma simplex the incidence is approximately equal: Priestley Smith in fact, reviewing a thousand glaucoma patients, found a slightly higher incidence of chronic glaucoma in men. Here too lies the explanation of why, in some cases, the administration of eserine has no effect in retarding the progress of optic atrophy though it may effectually prevent the occurrence of increased intra-ocular tension. Equally clear becomes the failure of operative interference in the same group of patients: the tension remains low but the optic atrophy progresses. In those cases where the factors of capillary stasis and increased permeability, and of the local accumulation of toxic waste products such as H-substances, choline and lactic acid, play an additional part, and give evidence of their presence in rise of tension, improvement is obtained by the release of stasis. The ischaemic factor is also improved in proportion to the lowering of tension, which improves the circulation by increasing the relative height of the blood pressure, but in cases in which the tension has never been raised this improvement cannot be obtained save at the cost of hypotony of the eyeball. On the other hand general elevation of the blood pressure can and will arrest the progress of optic atrophy. The dictum of Lauber applies with equal force to other types of ischaemic optic atrophy, such as tabetic, and it is interesting and relevant to note the work of Knapp (1928), who found optic atrophy associated with sclerosis of the basal cerebral vessels, and of Thiel (1932), who observed atrophy and cupping of the optic nerve with nasal field defects, indistinguishable from that of chronic glaucoma, as a result of sclerosis of the internal carotid arteries. These cases showed no rise of intra-ocular tension. A similar type of optic atrophy is reported by J. Jameson Evans (1938) in association with naevus flammeus and here again no increase of tension was noted over a period of four years' observation, while Reid (1937) confirms the fact of cupping with atrophy without rise of tension and considers that this is due to defective vascular nutrition of the lamina cribrosa. It will be recalled that the findings of Behr (1937), on the blood supply of the optic nerve here find support, and that the cupping of the disc and recession of the lamina cribrosa in fact constitute an example of staphyloma formation resulting from ischaemic degeneration of the sclera similar to that referred to already in respect of the equatorial region of the eye, though in these cases the factor of vaso-sclerosis is of major importance to that of capillary or venous stasis. Further study of the precise condition of the capillaries of the uvea and of the nutrient vessels of the optic nerve is required. At

present an investigation of this nature is being conducted, the vessels being stained by Pickworth's method (1938) (see Fig. 15). The present findings suggest that stasis will be shown in the uvea in congestive acute or sub-acute glaucoma; the conditions pertaining to chronic glaucoma remain to be considered. It becomes apparent that glaucoma without tension is a clinical entity: whether it is justifiable to give it the name of glaucoma is a matter for careful consideration and for future discussion, but chronic glaucoma simplex is in fact an ischaemic atrophy of the optic

Diagrammatic Scheme of Pathology of Glaucoma


CENTRAL NERVOUS SYSTEM
(Central Nervous System) (Hormone instability)
Emotion, etc. and Vaso-motor control
C
SY. PARA.
(Adr.) (ESER.)
P
Contributory local vascular factors.
Anti dromic Impulses or Long axon Reflexes.
Arteriosclerosis
HORMON. & BLOOD.
HEPARIN. CHOLESTEROL CALCIUM.
V
AXON. (HIST.)
PERIPHERY
Vessels
Hereditary Predisposition
Changes in uveal circulation.
Capillary dilatation: stasis and increased permeability. Loss of venous tone and congestion. Loss of arteriolar elasticity and tone. Accumulation of toxic metabolites (H-substances, CO_2, Lactic Acid).
(Anatomical Predisposition)
Defective nutrition of retina and optic nerve.
Swelling of vitreous. Increased protein content of vitreous and aqueous.
Stasis of venous return from ciliary region.
Loss of accommodation. Paresis of ciliary nerves. Dilatation of pupil. Corneal oedema.
Defective light/dark adaptation: loss of visual field: optic nerve atrophy and shrinkage (without rise of tension in some cases)
Obliteration of circumlental space: forward movement of iris-lens mass: obliteration of filtration angle.
Contributory anatomical factors.
Further retention due to obliteration of channels of drainage of intra-ocular fields
Disproportionately large lens.
Disproportionately small eye.
Increased size of senile lens.
Hypertrophy of ciliary processes in hypermetropia.
Congenital defects of filtration angle.
Sclerosis of trabeculae of ligamentum pectinatum.
Blocking of spaces of Fontana by pigment granules, flakes of exfoliated lens capsule, etc.
Passive congestion of ciliary processes: stasis in episcleral veins and canal of Schlemm.
Corneal oedema. Increased intra-ocular tension. Defective nutrition of retina and optic nerve (see column 3).

nerve, due, most probably, to defective nutrition of the nerve itself rather than to interference of the retinal blood supply (which may occur without tension), and may be associated in greater or lesser degree with those changes of stasis in the uveal circulation which give rise to acute congestive glaucoma. If one excludes chronic glaucoma as a separate disease one must not forget the importance of the same pathological changes in the uveal vessels, to wit arteriosclerosis and proliferation of the endothelium of the venules, and perivascular cellular deposits, as contributory factors in the pathology of acute congestive glaucoma, nor that the two processes are frequently so closely associated as to pass from one clinical picture to the other within a few hours.

Hence the mechanism of glaucoma may be presented schematically in the following manner. The essential changes in the uveal circulation are represented centrally. The results of these changes are shown in three columns below. The factors influencing the vessel tone are shown above subdivided into those affecting the central nervous system, the periphery and the blood contents. The diagram also shows the interaction of these factors upon each other. The upper diagram is derived from that by Evans and Evans in a paper delivered at the Oxford Congress in 1934. The influence of predisposing anatomical changes, and their relative importance, is indicated in relation to the first column of symptoms recognised clinically as congestive glaucoma.

The Course of Future Research

The course of further enquiry into glaucoma must therefore be directed towards the elucidation of the precise mechanism of those factors influencing the state of the optic nerve, and, where possible, towards their control or correction when diseased. A great deal of research has already been carried out in this respect particularly with regard to the state of the uveal circulation in acute congestive glaucoma. Speaking of this form of glaucoma, Magitot remarked " le glaucome est un oedème," and, in dealing with the end results or sequelae of the disease first, the release of oedema from the water-logged tissue spaces is a necessary procedure. Till recently this has been attempted chiefly by operative means such as cyclodialysis, iridencleisis and corneo-scleral trephining.

Effect of Release of Local Metalobites by Operative Means

These, however, are only means of supplying abnormal outlet to serous fluid and produce no actual effect upon the underlying condition of the capillaries apart from such benefit as may accrue

from a release of accumulated vaso-toxic metabolites in the tissue fluids. Poos (1938), who maintains that the initial lesion in congestive glaucoma is venous obstruction, leading to increased permeability and paralysis of the capillaries, also holds that the beneficial effect of operative interference is achieved by the release of toxic products of this paralysis. It is hoped that the instruments required for these operations will some day be found only in ophthalmic museums in memory of the dark ages of ocular pathology.

Septic Foci and Sources of Origin of Antidromic Impulses

Turning now to the correction of the underlying factors of circulatory disorder, one may consider first the correction of venous and capillary stasis. The peripherally seated agents responsible for antidromic impulses or long axon reflexes are fortunately to be found, in most instances, in the neighbouring organs, the nose, tonsils, sinuses and teeth. Elimination of all septic foci and sources of irritation must be ensured. The influence of such agents is often difficult to assess but the success, in such cases, of anaesthetising the appropriate ganglia, points to their influence being considerable. One may recall the association between Sluder's syndrome and glaucoma, and the effects of injection of the spheno-palatine ganglion in this connection.

Antidromic Impulses

It can be shown too that retrobulbar injection of novocaine will, through paralysis of the ciliary ganglion, effectively lower the intra-ocular tension, presumably by breaking the axon reflex or antidromic impulse, or perhaps by abolishing the excess of sympathetic tone in the innervation of the uveal blood vessels.

Retro-bulbar Injections

Experimental records on the varying effects of retrobulbar injections, in normal and glaucomatous eyes, of differing drugs, may provide an indication of the relative importance of distant nervous impulses as against purely local vaso-motor disturbance. For this purpose it might be profitable to use solutions of novocaine, novocaine and adrenalin, adrenalin, eserine, doryl, and doryl and eserine. Isotonic saline should form a suitable control.

Arterio sclerosis

The factor of arteriosclerosis cannot be entirely eliminated but precautionary treatment may be of some preventative value. Further histological evidence of the condition of the anterior and

posterior ciliary vessels is needed, particularly in relation to the circle of Haller in chronic glaucoma.

Heredity

The influence of heredity can hardly be corrected but the emotional diathesis of many patients in this group may be treated as a prophylactic measure.

Contents of Vessels

Consideration of the composition of the blood itself brings to notice in the first instance the hormones. The influence of hormones is a matter for further research from which one may hope to learn how to control and regulate the balance between the sympathetic and para-sympathetic tone of the blood vessels. In this field there lies the promise of restoration of one of the most frequent disorders which result in venous stasis and increased capillary permeability. It appears probable that the pituitary-thyroid-suprarenal triad will, between them, be found to control the tone of the blood vessels. Mossa (1934) concluded from his investigations that the thyroid alone influenced the intra-ocular tension, hypofunction causing a rise of tension. The hormones exert a pronounced effect on the emotional make-up of the patient and may be found to assume importance from this aspect in relation to hereditary predisposition. Fuchs (1924) and Lamb (1926) both contend that hormones influence the general condition of the circulation, so affecting the intra-ocular fluid. The association between the hormones, the disturbances of circulation during the menopausal and post-menopausal phase in women, and congestive glaucoma hardly needs to be emphasised. In connection with endocrine disturbance and its association with glaucoma, it may be noted that Salvati (1938) found an increase of the cholesterin content of the blood and holds that hypercholesterinaemia may be a predisposing cause towards the incidence of glaucoma.

Secondly one has to consider the thrombotic potential of the blood in glaucoma, particularly with reference to acute thrombotic glaucoma. The question arises whether the tendency to thrombosis is due to local disease of the vessel walls or is, in part at least, due to an excess of thrombokinase in the blood of such patients. The success of heparin therapy in a few cases of thrombosis of the central retinal vein indicates the need for investigation of acute glaucoma on similar lines. It is possible that, after a single attack of acute glaucoma the institution of heparin therapy might prevent further attacks, since it has been shown that patients of the glaucoma diathesis show a diminished serum

globulin and a diminished coagulation time. Further investigations of this nature may serve to indicate the precise nature and significance of these changes: research on the blood sedimentation rate may also prove of value though this is a less promising line of enquiry on account of the frequent presence of sepsis and other distorting factors.

Condition of the Blood Vessel Walls

Investigation of the condition of the blood-vessel walls is the next important step. As yet our information on the relative importance in glaucoma of the condition of the arteriole, capillary and venule respectively is far from complete. In this thesis it is held that all three are implicated: that in acute congestive glaucoma the process of venous and capillary stasis is of greater degree than that of arteriolar sclerosis or spasm, whereas, in chronic glaucoma simplex, especially in those cases without increase of tension, sclerosis of the small nutrient arteries of the anterior portion of the optic nerve is mainly responsible. Behr (1937) showed that the blood supply of the lamina cribrosa and of the anterior third of the optic nerve is derived from branches of the posterior ciliary arteries, and that the central artery of the retina gives no branches to this part of the nerve. Fig. 21 shows

FIG. 21.

Case: F.M —Chronic Glaucoma. Showing sclerosis of posterior ciliary vessels.

clearly the extreme sclerosis of the posterior ciliary vessels in such a case, obtained from a patient with long standing chronic glaucoma (F. M.).

One must emphasise that this hypothesis applies solely to the predominant vascular lesion and it must not be forgotten that the two conditions frequently coincide and that the influence of both together is frequently shown, especially in the ciliary body and in the episcleral vessels of the anterior ciliary region in cases of acute congestive glaucoma. The alteration of the condition of the blood-vessel walls is the basis for much of the modern treatment of glaucoma. It has already been suggested that the use of miotics such as eserine and pilocarpine is beneficial not, as was at first assumed, on account of the constriction of the pupil but through their vaso-constrictor action on the blood vessels throughout the uveal tract. Magitot (1921) has drawn attention to this action in discussing the intra-ocular tension. Recently considerable attention has been given to acetyl-choline, and to its derivative carbaminoyl-choline chloride known as doryl. The researches of Dale (1930-1934) and his co-workers showed that acetyl-choline appeared in general to produce effects of parasympathetic stimulation. Subsequently it has been shown that acetyl-choline is the transmitter of nervous impulses, both sympathetic and parasympathetic, to plain muscle, that it is destroyed at its situation between the nerve ending and the muscle fibre by esterase, and that it is prohibited from action by atropine which interposes itself between the acetyl-choline and the effector organ. The action of eserine is to prevent the destruction of acetyl-choline by esterase (Figs. 22 to 24). (Fraser, 1938.)

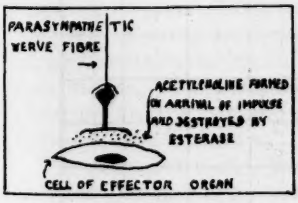

PARASYMPATHETIC
NERVE FIBRE
ACETYLCHOLINE FORMED ON ARRIVAL OF IMPULSE AND DESTROYED BY ESTERASE
CELL OF EFFECTOR ORGAN

FIG. 22

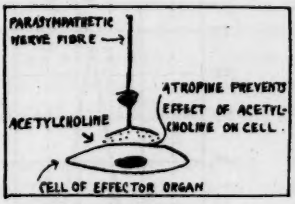


FIG. 23

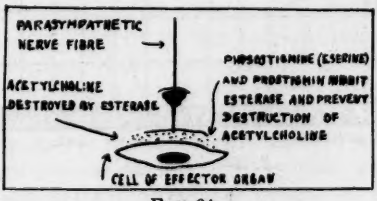
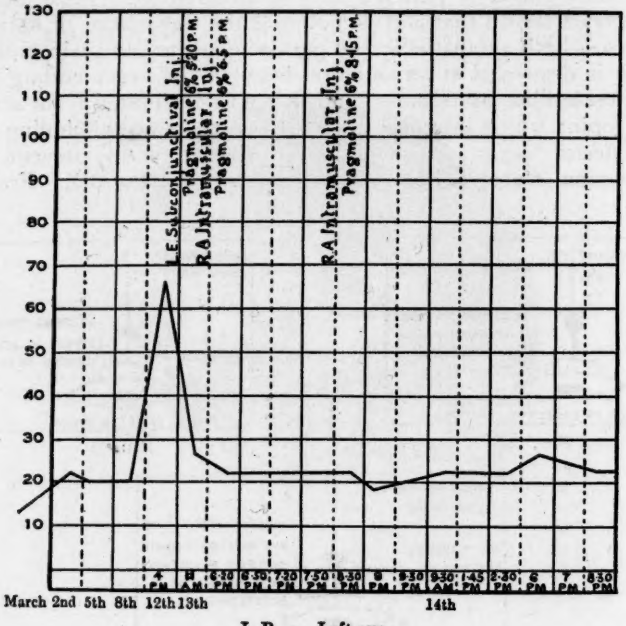

PARASYMPATHETIC
NERVE FIBRE
PHYSOSTIGMINE (ESERINE) AND PROSTIGMIN INHIBIT ESTERASE AND PREVENT DESTRUCTION OF ACETYLCHOLINE
ACETYLCHOLINE DESTROYED BY ESTERASE
CELL OF EFFECTOR ORGAN

FIG. 24.

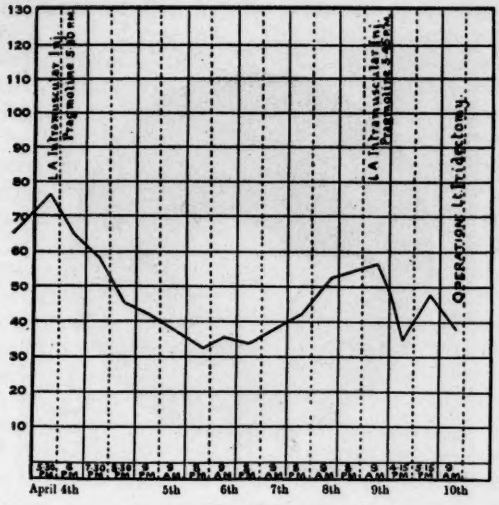
From Fraser, *Brit. Med. Jl.*, June, 1938.

The therapeutic effect of giving acetyl-choline by intramuscular injection is to influence the tone of the blood vessels in favour of a parasympathetic predominance, in contrast to the sympathetic predominance existing in acute glaucoma, thus producing dilatation of the arterioles, constriction of capillaries and improvement of venous tone. Evans and Evans (1934) reported cases treated by this method and found reduction of tension in some instances. They found, however, that the effects were evanescent and that it was difficult to obtain consistent activity of the drug, which is easily rendered inactive. Similar results were obtained by Velhagen (1934) who observed dilatation of the vessels of the ciliary processes and an increased secretion as shown by the sodium fluorescein test. Owing to uncertainty of action, the use of acetyl-choline has now been largely superseded by doryl which is a more stable compound and appears to have a more prolonged therapeutic effect. As might be supposed the influence of these drugs is most pronounced in cases of moderate disturbance of the balance of nervous tone control of the blood vessels. Illustration of this is given by these two tonometric charts of patients J. B.



J. B—. Left eye.

FIG. 25.



R. W—. Left eye.

FIG. 26.

and R. W., having initial tensions of 53 mm. and 58 mm. Hg Schiötz respectively. (Figs. 25 and 26.)

In the case of chronic glaucoma of long standing with optic atrophy the factor of sclerosis of nutrient vessels precludes such rapid or such marked effects. I have treated a number of patients of this group with injections of acetyl-choline (0·125 grm.) intramuscularly given twice a week, or weekly, for periods up to six months. During treatment the central fields and size and shape of scotomata were recorded monthly on a Bjerrum's Screen at two metres. Representative charts so obtained show that the changes on the whole were insignificant, though some slight improvement is shown.

The action of doryl, however, has been more encouraging. In particular it has been noted that this drug has a complementary action in conjunction with eserine. For instance cases occur in which eserine, given as drops, fails to control the raised intraocular tension completely: it has been found that the addition of 1 per cent. solution of doryl in equal proportion to a ½ per cent. solution of eserine has a markedly greater effect in these cases. The use of doryl by intramusclar injection is also more reliable but experience is as yet limited in this field. Further investigation on the correlated actions of doryl and eserine, and the best means of administration should provide a means of obtaining greater control of vessel wall tone.

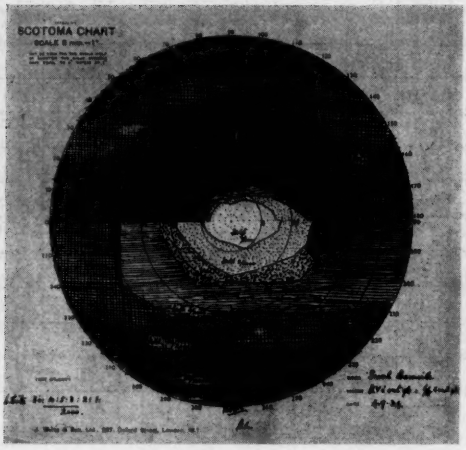


FIG. 27. September 4, 1934.

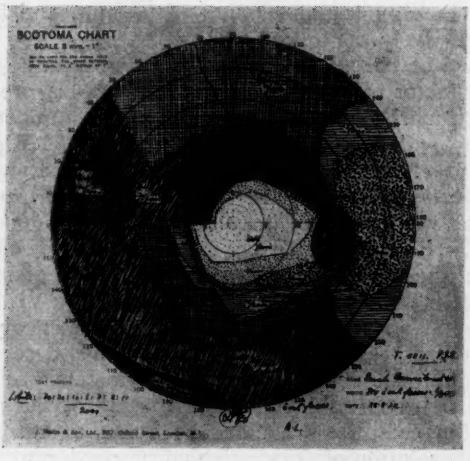


FIG. 28. August 26, 1935.

Case: *S.B.*—Eight months' treatment, at first bi-weekly; then weekly injections of Pragmoline ('125 grm.) intramuscularly.

Chemical means of altering the permeability of the capillaries also present a field of research. Mention has already been made of the experiments of Fischer, M. H., and Thomas who showed that increased acidity resulted in an increased intra-ocular tension which could be reduced by subconjunctival injections of sodium citrate. The influence of calcium salts on capillary permeability has also been studied and calcium has been given with a view to decreasing the permeability, but with indifferent success. Further research in the laboratory on the condition of the vitreous and of the uveal blood vessels may lead to more exact knowledge of the factors involved. In particular the specific gravity of the healthy (or at least non-glaucomatous) in contrast with the glaucomatous eye should be exactly determined: also the specific gravity, post-mortem, of healthy eyes before and after the addition of small amounts of lactic acid. The albumen content of the vitreous in glaucoma and in health is an investigation which is already under review. If possible, the question of whether an increase of H. substances in the uveal circulation accompanies the onset of an acute or subacute attack of congestive glaucoma with rise of tension needs to be determined. Clinically the precise action of short-wave therapy and of diathermy requires further investigation. The beneficial effect of short wave therapy applied locally in cases of iridocyclitis with secondary glaucoma has been the subject of articles by Lloyd (1938) and others. What precisely is the effect of short waves on the osmotic pressure of colloids and tissue membranes and on capillary permeability, and whether this form of treatment can be applied to acute congestive glaucoma remains to be discovered.

The matter of blood velocity is a further research which might indicate the relative proportion of vascular stasis or sclerosis in the varying clinical forms of glaucoma. Whether it will be possible to record alterations of temperature in the ciliary body, for instance, is doubtful but it is a subject which may well be within the reach of science in time to come.

The problem of the derivation of the aqueous humour must also be finally settled before the pathology of glaucoma can be considered completely known, and this can only be done by precise experiments on the exact conditions on each side of the ciliary epithelium in a large number of animals. If means should become available for the application of similar experiments to man the problem would be more easily resolved.

And there, for the moment, the problem of glaucoma rests. While the present conception of this clinical syndrome or symptom complex is very different from that of fifty years ago one cannot forget how much of our present knowledge is due to the work of those previous workers, who enjoyed few of the advantages, both clinical and experimental, which we now enjoy, but excelled at least in detailed observation and constant zeal.

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ANNOTATION

The Distribution of Sulphanilamide in the Eye.

Chemotherapy for certain inflammatory diseases of the eye such as ophthalmia neonatorum, some forms of chronic conjunctivitis including trachoma and pemphigus, and endogenous infections such as uveitis and panophthalmitis is at present *sub judice.*

The experiments of Bellows and Chinn* have made an interesting contribution to this matter. Their work has shown the distribution of sulphanilamide in the various ocular tissues after the administration of a single dose by the mouth and following divided therapeutic doses; the action of heat and other chemicals on the concentration of sulphanilamide in the aqueous humour and the effects of local application of this drug to the eye by dusting it on to the conjunctiva and cornea and by subconjunctival injection of it in solution.

From the results in experimental animals it seems that the ocular tissues are rapidly penetrated by the drug, traces of which are found throughout the eye 15 minutes after oral administration. The rapidity of penetration depends upon the relative vascularity of the tissue; for instance the concentrations of sulphanilamide in the various ocular tissues occur in the following order: chorio-retinal tissues, corneo-scleral tissues, aqueous, lens and vitreous. The maximum concentrations were reached in the corneo-sclera at the end of four hours; in the blood, aqueous and vitreous at the sixth hour; and the lens, choroid and retina at the twelfth hour. The most rapid rise of tissue concentration was between the second and third hours after injection, with the exception of the lens, in which this occurred between the fourth and sixth hours. The fall in concentration was the most precipitous in those tissues which contained a relatively considerable amount of the drug, but the lens in which there was a low distribution retained at the end of 48 hours more than three times the amount of sulphanilamide in each of the other ocular tissues.

Animals' eyes were removed for estimation of the content of the drug in various ocular tissues at the end of one, two, four and six days during the administration of therapeutic doses of sulphanilamide, 0·075 gm. per kilo. of body weight given daily in four divided doses at 8 a.m., 12 noon, 6 p.m. and 10 p.m. The highest concentration was 3·5 mgm. per 100 c.c. of blood at 10 p.m. and the lowest 1·4 at 8 a.m., the latter being the time at which the eyes were excised. These readings are below the blood level of 5-10 mgm. per 100 c.c. advocated for therapeutic action. The estimations of the tissue concentrations of sulphanilamide showed that the fall

*Bellows, J. C. and Chinn, H., *Jl. Amer. Med. Assoc.*, Vol. CXII, 2023, 1939.

from 6 to 12 hours after administration was very slight, a fact which suggests that the administration of the drug in doses twice daily (at 9 a.m. and 5 p.m.) as advocated by Bellows and Chinn would be as effective as four times a day.

The administration of heat and such chemicals as ethyl morphine hydrochloride, atropine and physostigmine had no effect on the concentration of sulphanilamide in the aqueous but acetyl—β—methylchlorine chloride (mecholyl) caused through its power to alter capillary permeability, an increased concentration of the drug over the control values. Paracentesis of the anterior chamber followed half-an-hour later by another paracentesis also leads to an increased concentration of sulphanilamide in the aqueous.

Sulphanilamide dusted on to the conjunctiva and cornea lead to some irritation without any appreciable penetration of the drug into the ocular tissues. After subconjunctival injection of a solution of the drug the aqueous concentration was far below that which followed oral administration.

Bellows and Chinn found sulphanilamide in the tears of two patients who were receiving 3 grm. a day. In one instance the tears contained 1·5 mgm. in 100 c.c., 3 hours after the administration of 1 grm. and in the other 17 hours after a similar dose, the concentration was 0·8 mgm. per 100 c.c.

It is evident from these experimental and clinical findings that the ocular tissues are penetrated by sulphanilamide.

ABSTRACTS

I.—OPERATIONS

(1) **Valerio (Milan).—The surgical treatment of ptosis, with special regard to Nida's operation. (Contributo allo studio del tratamento chirurgico della ptosi palpebrale con particolare riguardo all'introduzione del la tecnica di Nida).** *Rass. Ital. d'Ottal.*, January-February, 1939.

(1) The first part of this paper is a short review of the various measures which have been taken to correct the deformity of ptosis; **Valerio** points out that if the superior rectus is undeveloped, the frontalis may be employed to help to raise the lid but that the relation between movement of the eye and lid will not be normal; there must, therefore, be different methods employed according to the state of the external ocular muscles. Motais was the first to bring the superior rectus into play when the levator palpebrae is wanting; his operation is not very easy to perform and the author

draws attention to an operation devised by Nida which is simple and effective. It consists in laying bare the tendon of the superior rectus and lifting it on a hook. Then a strip is cut from the upper border of the tarsal plate about 2 mm. in width in the centre and 3 mm. at the ends; this is freed but left attached to the lid at the outer end; a second hook is passed under the superior rectus tendon, the tarsal slip is passed under the tendon and the end secured to its bed, and the operation is over. This secures the lid to the globe and the two structures move together. The author has performed the operation on several occasions and is very pleased with the result. He says, also, that in the case of Gunn's syndrome he anchored the lid to the eye in this way and the appearance of the patient was much improved. The one disadvantage, which he does not mention, would seem to be the implantation of a strip of conjunctival tissue under the tendon and the possible formation of a cyst in that situation.

A similar operation was worked out some years ago by R. Affleck Greeves. A description of it will be found in "Handbook of Ophthalmology." Neame and Williamson-Noble (J. & A. Churchill, 3rd Edition, 1939) p. 247.

HAROLD GRIMSDALE.

(2) **Jaensch, P. (Essen).—The operative treatment of isolated bilateral paresis of the superior obliques. (Die operative Behandlung der isoleirten doppelseitigen Trochlearisparese).** *Klin. Monatsbl. f. Augenheilk.*, Vol. CII, p. 305, 1939.

(2) **Jaensch** describes the treatment of a case of paresis of both superior oblique muscles, which caused marked head tilting and extensive diplopia. A recession of the right and left inferior recti was done in turn, followed by myomectomy of the left inferior oblique. The final result was excellent and the patient was able to return to work. The records of the residual diplopia after each operation are very interesting.

D. R. CAMPBELL.

(3) **Reitch, W. (Hirschberg).—Sklerenkleisis. (Sclerencleisis).** *Klin. Monatsbl. f. Augenheilk.*, Vol. CII, p. 326, 1939.

(3) **Reitsch** describes an operation which he has tried in a few cases of persistent glaucoma. A narrow tongue is cut from half the thickness of the sclera and is turned down and tucked through a small wound at the limbus, so that it projects well into the anterior chamber. The wound is covered with conjunctiva as in a trephine operation.

D. R. CAMPBELL.

(4) **Schmidt, J. (Pees).—The technique of keratoplasty. (Zur Technik der Hornhaut plastik).** *Klin. Monatsbl. f. Augenheilk.*, Vol. CII, p. 315, 1939.

(4) **Schmidt** suggests that the hand trephine is more satisfactory than the motor trephine. The latter seems to cut the corneal endothelium irregularly and a clear corneal graft is spoilt later by a membrane growing across the back of the cornea.

D. R. CAMPBELL.

II.—TRACHOMA

(1) **Cuenod, A. and Nataf, R. (Tunis).—Trachoma and Rickettsia. (Trachome et Rickettsies).** *Ophthalmologica*, Vol. XCVII, p. 277, 1939.

(1) **Cuénod** and **Nataf** report briefly the morphological and experimental researches on trachoma carried out during the past few years. These researches would suggest that the effective trachoma body or agent should be ranked near to the family of the Rickettsia, some of the characteristics of which it possesses although differing therefrom in other respects. Since, however, the definition and classification of the Rickettsia has not been clearly achieved, they suggest that it is preferable to use the expression "Rickettsoid body" instead of trachoma Rickettsia, and propose that the virus body of trachoma be called "Prowazekia Trachomatis" whereby the work of Prowazek would be honourably acknowledged without anticipating a definite classification.

ARNOLD SORSBY.

(2) **Lagomarsino (Genoa).—Bee venom in the treatment of trachoma. (Il veleno delle api nella cura del tracoma).** *Ann. di. Ottal.*, February, 1939.

(2) After a discourse on the nature of bee venom and the method of collecting it, the author gives the results of the treatment of 20 cases of trachoma. She made use of "tracocid" a preparation of bee venom which must be mixed before use with an anaesthetic; this is injected subconjunctivally. She claims great benefit in almost all cases.

HAROLD GRIMSDALE.

(3) **Moretti (Catania).—Splitting the conjunctiva in trachoma. (Contributo alla cura chirurgica del tracoma; "los doppiamento congiuntivale").** *Rass. Ital. d'Ottal.*, January-February, 1939.

(3) **Morretti** claims that by the method described in this paper, he is able to secure a more rapid production of scar

tissue of the upper cul-de-sac and a higher percentage of cures. He does not claim constant success. The method of his new plan is as follows: he anaesthetises the conjunctiva by an injection of pressocain followed by instillation of pressocain and dionin. The tissues of the cul-de-sac are swollen by this, and it is easy to evert the upper lid; this shows a number of granules in various stages; by means of the roller-forceps the granules are crushed and emptied; then with a sharp spoon all the conjunctiva of the tarsus and upper cul-de-sac is lightly scraped. The lower lid and the caruncle share in this. After this a small cut is made with scissors, vertically, about 2 or 3 mm. long, as near the outer angle of the lid as possible and in contact with the upper edge of the tarsus. Then a thin spatula is passed through the opening, towards the other end of the tarsus, and by slow and gentle movements the upper layer of the conjunctiva is separated from the deeper. Care must be taken that this splitting goes to the upper edge of the tarsal plate. The after treatment is the application of tannic acid in ointment and daily touching the conjunctiva lightly with sulphate of copper. After two or three weeks, the conjunctiva of the fornix loses its red colour and takes on the characteristic look of scarring.

When there is pannus, the author passes a suture round the cornea subconjunctivally, leaving the ends long and secured outside the commissure by means of plaster. If there is ulceration of the cornea, copper sulphate must not be used in the after-treatment which will consist in the use of an ointment of atropine and xeroform. It will be seen that the name "splitting of the conjunctiva" is chosen as representing the new factor in the treatment; the crushing and scraping, though essential parts, are not mentioned by name.

HAROLD GRIMSDALE.

III.—MISCELLANEOUS

(1) **Bonnefon, G. (Bordeaux).—The treatment of eyes affected by mustard-gas. ("L'Oeil Ypérité: son traitement").** From *La Gazette hebd. des sc. Med. de Bordeaux*, No. 11 and 12, March, 1939.

(1) In a short but interesting paper, **Bonnefon** discusses the conclusions which he came to after having experience in the treatment of some 3,600 eyes affected by mustard-gas, during September, 1918.

After a short survey of the clinical picture met with in these cases, the author puts forward a strong and logical case for

the adoption of a therapy based on the use of the "hypertonic ocular bath."

Firstly, he points out that copious douching is unnecessary for superficial washing of the mucous surfaces, as this is achieved by the reflex flow of tears, and useless in so much as it does not reach the intracellular caustic.

The essentials of the author's method are then as follows:—

1. To encourage the washing action of the tears, he suggests that at the First Aid Post, the patient should be given a basin of warm water and some cotton-wool, with directions for use by himself. He would then keep bathing the lids to prevent them becoming adherent, and thus encourage a continuous flow of tears.
2. On arrival at the Casualty Clearing Station, or First Reception Hospital, the hypertonic ocular bathing would be commenced. The author recommends the following solution:—

Sod. sulphate to saturation -	800 grammes.
Syrup of sugar - - -	200 grammes.

The solution is used in an eye-bath, and as proof of its efficacy the author states, that after ten minutes immersion, the water in the bath is found to be caustic. The mechanism of osmotic drainage having come into play. He also points out that with 200 baths and four nurses, 1,500 eyes can be bathed twice a day with ease.

The continuation of this treatment is advised as long as there are any signs of photophobia or lacrymation. From his experience during the Great War, Bonnefon is convinced that the "osmotic bath" is the only effective way of banishing rapidly the irritant sequelae of these injuries. The author also stresses the danger of using cocaine ("that enemy of the corneal epithelium") to alleviate pain in these cases.

Ointments would also seem to be contra-indicated, as they tend to hold up the flow of tears, and are also accumulators of mustard-gas on account of the latter's high solubility in the hydrocarbon oils and animal fats.

The use of 2 per cent. dionine is recommended and a prescription is given for a hypertonic solution to be injected subconjunctivally in severe cases.

G. I. SCOTT.

(2) **Purtscher, E. (Graz).—The aetiology of spontaneous detachment of the choroid and of serous Tenonitis. (Zur Aetiologie der "spontanen" Aderhautabhebung und der "serosen Tenonitis").** *Zeitschr. f. Augenheilk.*, Vol. XCIV, p. 12, 1938.

(2) **Purtscher** describes the case of a man, aged 67 years, who showed bilateral Tenonitis followed by choroidal detachment,

eventually leading to spontaneous recovery. He disputes the conception that the space of Tenon is to be regarded as a synovial cavity subject to the same rheumatic manifestations as joint cavities. He holds that Tenonitis is a vasomotor neurosis, similar to posterior scleritis and episcleritis fugax. It is not an independent disease, but a result of episcleral inflammation. In view of his findings he stresses the need for searching for choroidal detachment in Tenonitis.

ARNOLD SORSBY.

(3) **Siegert, Peter (Hamburg).—On melanosarcoma of the iris. (Ueber Melanosarkome der Iris).** *Arch. f. Ophthal.*, Vol. CXXXIX, p. 591.

(3) **Siegert** here describes in detail three cases of sarcoma of the iris showing different stages of development; two of these had been followed clinically.

The evidence of malignancy in these neoplasms is discussed at length, and in this connection he points in case 1 to the infiltrating mode of growth, a proliferation of cells not seen in either naevus or melanoma, and the enormous variation in the type and pigmentation of the cells. This variability in the cells (together with signs of karyokinesis and metastasis), in case 2 is also commented on. In these too there was an "oedema" or swelling of the most superficial cells of the iris next the aqueous fluid that is not found in benign naevus.

The exact origin of the sarcoma cells it is often difficult to decide. In case 1 there was no direct connection with the ectodermal pigment layer, while the pigmentation of the melanoblasts differed widely from that of the pigment epithelium. In case 3 no real difference was noted between the melanophores in the iris and the pigment epithelium. The author inclines to the view that these cells are mesodermal in origin. He also emphasises the fact that a malignant neoplasm may progress and yet may give rise to no symptoms or be recognised clinically, while on the other hand tumours which cause blindness from glaucoma may fail to show anatomically the characteristic features of malignancy (destructive growth and metastasis).

Metastasis in these slowly growing tumours occurs primarily by way of the perivascular lymph spaces not by the circulation or the aqueous fluid.

THOS. SNOWBALL.

(4) **Bencini (Siena).—Six cases of sympathetic ophthalmia. (Considerazioni clinico-istologiche-terapeutiche sopra sei casi di oftalmia simpatica).** *Boll. d'Ocul.*, May, 1939.

(4) In this paper is recorded the course of six cases of sympathetic ophthalmia in five of which the exciting eye was

examined microscopically after removal. The sixth case had the exciting eye removed before he came under **Bencini's** care. In two, the marked symptom was a papillo-retinitis, and in these the ciliary nerves were specially concerned in the inflammatory process. The author thinks that this may point to the presence of a neurotrophic virus, In all the cases, the main treatment was the intravenous injection of urotropin, with large doses of sodium salicylate. In the latter cases the urotropin was combined with chinophenyl (phenynchinolin-carbonic acid) which, he says, has helped much. In all cases the result was good; in one, there was relapse after apparent cure, and secondary glaucoma followed. In this case treatment was prolonged over seven months. In all, the exciting cause was a wound with prolapse of some part of the uveal tract; in one case, the second eye showed signs of sympathetic inflammation on the 15th day after the original injury; in two, enucleation preceded the onset of sympathetic in one case by 10 days and by 11 days in the other. The author thinks that all our knowledge points to the action of a virus in this disease. He has attempted to provoke herpes in the cornea of a rabbit by inoculating it with material from one of his cases, but without success. He concludes that the virus of herpes is not the cause of sympathetic inflammation. (Von Szily had been able to show that inoculation of the uveal tract of an animal with the virus of herpes, produced a form of inflammatory reaction with infiltration of the choroid by eosinophilis and leucocytes which could be passed from animal to animal).

HAROLD GRIMSDALE.

BOOK NOTICES

Atlas Clinique d'Ophtalmoscopie Photographique. By HENRI TILLE and A. COUADAN. Pp. 194, 202 Illustrations. Masson et Cie., Paris. 1939. Price, 280 francs.

The findings of the ophthalmoscope, the slit-lamp and corneal microscope when correlated ultimately with microscopic evidence of morbid histology give to ophthalmology a precision which is both exquisite and scientific. The development of the technique of fundus photography is yet a step further in recording the truth. It lacks some of the imperfections and omissions of the artist whose observations are set down by drawing and painting and it also affords an admirable means of recording from time to time a changing picture of pathological events and thus of following up with accuracy the course of disease.

This atlas is beautifully composed. The reproductions of fundus photographs are admirable and are well set on the right page throughout the work. On the left page there is beside the title (and its English translation) a clinical resumé of the case, a description of the fundus findings and an interpretation of the photographic appearances of the lesions. Directional arrows placed vertically and horizontally indicate clearly at their point of section the site of the lesion referred to.

It is interesting to note that even optical artefacts and retinal "reflexes" particularly in young persons may have some significance by an alteration in their intensity or conformation.

The authors have attempted some clinical re-grouping based on photographic results. As a preliminary, to each chapter devoted to certain pathological groups there is a brief description in general terms of the nature of the lesions encountered and their aetiology.

The whole work is richly documented. The illustrations have been chosen from 2,000 photographs taken in ordinary light, colour and infra-red illumination. The cameras used have been of the Zeiss and Nordenson pattern, and the plates Agfa and Ilford rapid, 4·5×6. The exposure 1/10 to 1/5 second, and the reproductions made on copper engraving thread. The size of the retinal images is recorded in terms of optic disc diameters.

There is also a strip of cinematograph photos to show pulsation of the central retinal artery. The authors are to be congratulated on an excellent piece of work and a great contribution to ophthalmic literature. The reproduction, printing, paper and binding are also of a high quality.

Vias del Nistagmus. By Dr. BAUDILIO COURTIS. Pp. 150 with 93 microphotographs. Buenos Aires: Aniceto Lopez. 1938. Price unstated.

This monograph, the thesis "de profesorado" of the author, reviews the previous work on nystagmus in a historical manner from John Hunter in 1786 to Ohm in 1912-1917 and Argañaraz in 1924. The author then gives a classification under three headings: "reflex, vestibular, and central nystagmus"; and abstracts anatomical and experimental work on the nervous pathways in nystagmus. In Dr. Courtis's opinion nystagmus is a reflex phenomenon. There is a bibliography of 82 items and the monograph is profusely illustrated. Many of the microphotographs are extremely well reproduced and author and printer alike are to be congratulated on an excellent piece of work.

CORRESPONDENCE

ON THE TREATMENT OF MUSTARD GAS BURNS IN THE EYE

To the Editors of THE BRITISH JOURNAL OF OPHTHALMOLOGY.

DEAR SIRS,—The writer of a leading article in the *British Medical Journal* for November 4, 1939, makes the following statement:—In the improved protective measures rather than in improved methods of treatment lies the hope of counteracting the effects (of mustard gas on the eyes); for treatment of a gas injury, whether brought about by vapour or by liquid comes up against the fundamental difficulty that the effect of gas on a tissue is instantaneous, though there is some evidence that the prophylactic use of chlorinating agents will render a gas injury to the eye less serious.

The above statement may be timely in view of possibilities in the near future which may affect the civilian population as well as the members of the armed forces of the Crown.

There is some danger that enthusiastic ophthalmologists may advise remedies which will not assist nature. To take one instance, the application of cocaine, to alleviate pain, blepharospasm and the fear of impending blindness. One disadvantage of cocaine is the possibility of desiccation and exfoliation of the corneal epithelium, but the proponents of this form of therapy point to the alternative drugs pantocaine and procaine which do not threaten the cornea to the same degree. It is probably inadvisable, however, to use any local anaesthetic, (1) on account of the danger that the sufferer may himself cause damage to his cornea by friction with his finger directly or through the eyelid; (2) because the profuse outpouring of lacrimal fluid with its isotonicity and lysozyme content is probably the best bland lotion available, and an efficient local anaesthetic will diminish this beneficial result.

The other important question is whether any irrigation at all is desirable and, if so, whether such a measure should be carried out frequently and for long periods at a time. On the one hand there is experimental evidence which was quoted at the British Medical Meeting in Aberdeen that a drop of mustard gas oil applied to the animal cornea causes instantaneous damage, and that even immediate irrigation makes no difference to the subsequent result. Similar experimental results are also reported by Brevet-Col. L. T. Poole (*Brit. Med. Jl.*, p. 972, 11 : XI : 39). On the other hand, it has been noticed that the effect of gas on animals without lacrimation powers, such as the horse and mule, is more apt to produce extensive corneal damage than in man. M. Bonnefon also in his

paper (an abstract of which appears on p. 788) remarks that even some time after treatment has begun, the solution used for irrigation may become caustic. This statement needs confirmation before acceptance.

With regard to M. Bonnefon's statement of the value of hypertonic solution, it will be well to keep an open mind on the subject and to try its effect on certain cases, but one must remember that in ordinary clinical work, a hypertonic remedy in the form of a half-saturated solution of magnesium sulphate has been extensively tried in cases of corneal ulceration and the results have not been especially convincing. Again M. Bonnefon in his paper lauds dionine as a useful accessory, but there are ophthalmologists of experience who can say that they have never seen any certain evidence that dionine has any therapeutic effect whatever as an ocular remedy.

Probably Sir William Lister has had a greater experience of the early stages of gassed eyes than anyone else in this country, and I hoped that he would have written for the Journal on this very important matter. He, however, says that he wrote his opinion fully in the Official History of the War and sees no reason to add to his views therein expressed. That article should be read by all those who are likely to have cases under their care. (*Vide* Official History of the Great War, Medical Services, Surgery of the War, Vol. II, pp. 529-540.)

In that portion of the chapter which deals with treatment he lays stress on the psychological value of separating the eyelids, and of thus convincing the patient that his sight has not been irreparably damaged. In mild cases a bland lukewarm solution was used for frequent gentle bathing; he thought that weak boric acid was as good or better than the 2 per cent. solution of sodium bicarbonate which was usually prescribed. Liquid paraffin was dropped into the eyes three times a day. In severe cases with pain and lid spasm, atropine ointment 1 per cent. as early as possible often gave marked relief.

If there were much conjunctival discharge, a weak solution of one of the organic silver compounds was instilled twice daily and was very efficient. It was inadvisable on account of the swelling to attempt eversion of the eyelids. These silver solutions were used especially when a corneal haze threatened ulceration. If the haze was overlooked, and silver was not used, severe infective ulceration was liable to occur, and Sir William Lister still emphasises the importance of this precaution. The eyes of course were not bound up, a frontal shade or dark glasses giving sufficient protection.

During convalescence, astringent drops of boric (2 per cent.) and zinc sulphate ($\frac{1}{4}$ per cent.) were instilled three times daily as soon as possible, the shade or dark glasses were dispensed with. Any

neurasthenic tendency had to be combated by vigorous mental environment, fresh air, tonics and suitable occupation.

One may add then that it will be well to be cautious in the treatment of these cases. Any excessive irrigation is more likely to damage the delicate corneal epithelium than to get rid of any residual poison. It may be found that the use of cod liver oil (with or without glucose) will be found useful (as suggested in Professor Burn's letter, *Brit. Med. Jl.*, November 11, 1939, p. 972) in place of liquid paraffin. It may also be found that a mild antiseptic such as acriflavine in oil ($\frac{1}{1000}$) or mercurochrome in water (2-4 per cent.) will be as effective in preventing sepsis as the organic silver compounds.

In conclusion one must emphasise again that prophylaxis is the best treatment. Some 20 years of experimentation is stated to have gone to the making of the service gas mask, and it is certain that the eyes and respiratory passages can be protected efficiently by the help of this apparatus. It remains for officers and instructors to see that the necessity for its use is impressed emphatically upon the minds of those under their care. Medical men may play their part in speaking of the need for this precaution. They would do so more readily if they could see the late results of the gassed eye casualties from 1917-18. There are nearly two hundred cases of severe defect of vision from late ulceration known in this country, and the total is still rising annually.

I have the honour to remain, Sirs,

Yours obediently,

FRANK JULER.

LONDON, W.1
November 11, 1939.

NOTES

Death

THE death of Professor Harvey Cushing on October 7, 1939, should not pass unnoticed in an ophthalmological journal, for his work on cerebral surgery and especially on pituitary tumours has had the greatest influence on the treatment of this type of case which frequently comes first under the notice of the ophthalmologist.

Cushing was the son of a doctor and was born in Cleveland, Ohio, on April 8, 1869. He was educated at Yale and Harvard where he took his M.D. in 1895. At the Johns Hopkins Hospital in Baltimore he filled several minor appointments before proceeding overseas for post-graduate study under Kocher, of Berne. On his

return to America he was for a time attached to the Johns Hopkins Hospital and later became Professor of Surgery at Harvard University. In 1932 he went to Yale as Professor of Neurology. Besides neurological surgery Cushing was a keen student of the history of medicine and his Life of Sir William Osler is a classic.

On his 70th birthday, this year, he was presented with a bibliography of his writings. Among the numerous honours which he received should be mentioned the C.B. (Military), the Legion d'honneur, the F.R.S., the Hon. F.R.C.S. England, Edinburgh and Ireland, and the Lister Medal.

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Honour

BRITISH ophthalmology will wish to congratulate Dr. H. M. Traquair on his election as President of the Royal College of Surgeons of Edinburgh for the ensuing year.

* * * *

The Wrong Bottle

WE have been sent the following note by one who wishes to remain anonymous. "A patient, erroneously in the dark, used in an eye-bath undiluted 'dettol' solution, instead of an eye-lotion. The immediate pain was acute. A doctor instilled cocaine and castor oil. Severe pain lasted about 12 hours and minor pain for four days. The corneal epithelium showed oedema; the lower bulbar and palpebral conjunctiva remained very red, and there was purulent discharge for about four or five days. The eye had practically recovered in eight days and was normal in ten days. Weak atropine drops and a simple lotion were used."

It is always easy to be wise after the event and we suppose that most of us at some time or another have taken up the wrong medicine bottle by mistake. The patient was lucky in that the results were no worse. This narrative adds another item to the growing list of "black-out" accidents.

FUTURE ARRANGEMENTS

December 9, 1939.—North of England Ophthalmological Society, at Leeds.

February 3, 1940.—North of England Ophthalmological Society, at Liverpool.

March 16, 1940.—North of England Ophthalmological Society, at Sheffield.

May 4, 1940.—North of England Ophthalmological Society, at Newcastle-on-Tyne.

July 4-6, 1940.—Ophthalmological Congress, at Oxford.